

WO9965908

**Title:
PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS**

Abstract:

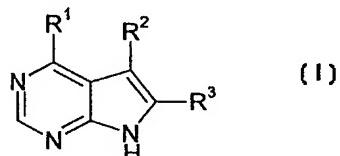
A compound of formula (I) wherein R₁; R₂; and R₃ are as defined in the description, and are inhibitors of the enzyme protein tyrosine kinases such as Janus Kinase (3) and as such are useful therapy as immunosuppressive agents for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other autoimmune diseases.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :	A1	(11) International Publication Number: WO 99/65908 (43) International Publication Date: 23 December 1999 (23.12.99)
C07D 487/04, A61K 31/505 // (C07D 487/04, 239:00, 209:00)		
(21) International Application Number:	PCT/IB99/01100	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date:	14 June 1999 (14.06.99)	
(30) Priority Data:		
60/089,866	19 June 1998 (19.06.98)	US
60/104,787	19 October 1998 (19.10.98)	US
(71) Applicant (for all designated States except US):	PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).	
(72) Inventors; and		Published
(75) Inventors/Applicants (for US only):	BLUMENKOPF, Todd, Andrew [US/US]; 9 Fairway Lane, Old Lyme, CT 06371 (US). FLANAGAN, Mark, Edward [US/US]; 10 Queen Eleanor Drive, Gales Ferry, CT 06335 (US). BROWN, Matthew, Frank [US/US]; 66 Greenhaven Road, Pawcatuck, CT 06379 (US). CHANGELIAN, Paul, Steven [US/US]; 4 Squirrel Lane, East Greenwich, RI 02818 (US).	With international search report.
(74) Agents:	SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).	

(54) Title: PYRROLO[2,3-d]PYRIMIDINE COMPOUNDS



(57) Abstract

A compound of formula (I) wherein R¹, R² and R³ are as defined in the description, and are inhibitors of the enzyme protein tyrosine kinases such as Janus Kinase (3) and as such are useful therapy as immunosuppressive agents for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other autoimmune diseases.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon	KR	Republic of Korea	PL	Poland		
CN	China	KZ	Kazakhstan	PT	Portugal		
CU	Cuba	LC	Saint Lucia	RO	Romania		
CZ	Czech Republic	LI	Liechtenstein	RU	Russian Federation		
DE	Germany	LK	Sri Lanka	SD	Sudan		
DK	Denmark	LR	Liberia	SE	Sweden		
EE	Estonia			SG	Singapore		

5

PYRROLO[2,3-d]PYRIMIDINE COMPOUNDSBackground of the Invention

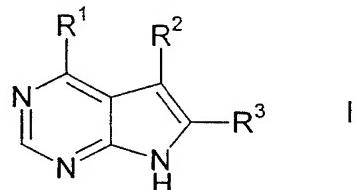
The present invention relates to pyrrolo[2,3-d]pyrimidine compounds which are inhibitors of protein tyrosine kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as JAK3) and as such are useful therapy as immunosuppressive agents for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia and other indications where immunosuppression would be desirable.

This invention also relates to a method of using such compounds in the treatment of the above indications in mammals, especially humans, and the pharmaceutical compositions useful therefor.

JAK3 is a member of the Janus family of protein tyrosine kinases. Although the other members of this family are expressed by essentially all tissues, JAK3 expression is limited to hematopoetic cells. This is consistent with its essential role in signaling through the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 by non-covalent association of JAK3 with the gamma chain common to these multichain receptors. XSCID patient populations have been identified with severely reduced levels of JAK3 protein or with genetic defects to the common gamma chain, suggesting that immunosuppression should result from blocking signaling through the JAK3 pathway. Animal studies have suggested that JAK3 not only plays a critical role in B and T lymphocyte maturation, but that JAK3 is constitutively required to maintain T cell function. Modulation of immune activity through this novel mechanism can prove useful in the treatment of T cell proliferative disorders such as transplant rejection and autoimmune diseases.

Summary of the Invention

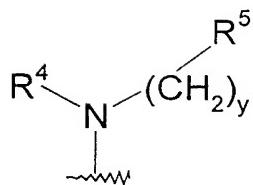
The present invention relates to a compound of the formula



30

or the pharmaceutically acceptable salt thereof; wherein

R¹ is a group of the formula

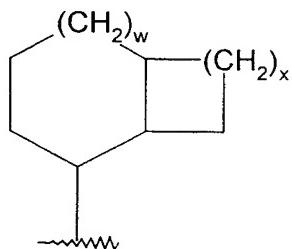


wherein y is 0, 1 or 2;

- R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;
- 15 R⁵ is selected from the group consisting of trifluoromethyl(C₁-C₆)alkyl, (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m,
- 25 R¹⁵R¹⁶NS(O)_m (C₁-C₆)alkyl, R¹⁵S(O)_m R¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or R⁵ is (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₂-C₆)alkoxy(C₁-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio(C₁-C₆)alkyl,
- 30 C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one to five cyano, nitro, halo, deuterium, hydroxy, carboxy, (C₁-C₆)acylamino, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, (C₁-C₆)alkylamino(C₁-C₆)acyl or ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl; or R⁵ is R¹³CO(C₁-C₆)alkyl or R¹³CO(C₃-C₁₀)cycloalkyl wherein R¹³ is R²⁰O or R²⁰R²¹N wherein R²⁰ and
- 35

- 5 R²¹ are each independently selected from the group consisting of hydrogen, deuterium, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₅-C₉)heteroaryl(C₁-C₆)alkyl; or R⁵ is R¹⁴, R¹⁴(C₁-C₆)alkyl or R¹⁴(C₃-C₁₀)cycloalkyl wherein R¹⁴ is (C₂-C₉)heterocycloalkyl, (C₁-C₆)acylpiperazino, (C₆-C₁₀)arylpiperazino, (C₅-C₉)heteroarylpiperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, 10 piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidinyl, (C₆-C₁₀)arylpiperidyl, (C₅-C₉)heteroarylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperidyl or (C₁-C₆)acylpiperidyl;

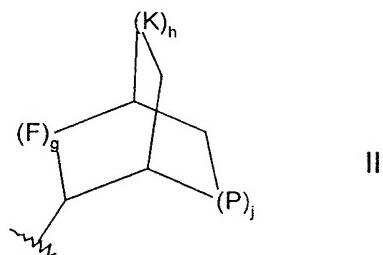
or R⁵ is a group of the formula



15 wherein w is 0, 1 or 2;

x is 0, 1, 2 or 3;

or R⁵ is a group of the formula

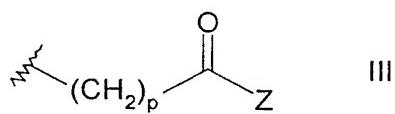


wherein g, h and j are each independently 0 to 3;

20 F, K and P are each independently oxygen, S(O)_d wherein d is 0, 1 or 2, NR⁶ or CR⁷R⁸;

R⁶ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl (difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₂-C₆)alkyl, (C₁-C₆)acyloxy(C₂-C₆)alkyl, (C₁-C₆)alkoxy(C₂-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl.

- 5 $\text{C}_{10}\text{arylthio}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfinyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylsulfinyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylsulfonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, amino($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)alkylamino($\text{C}_1\text{-}\text{C}_6$)alkyl, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $\text{R}^{13}\text{CO}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ wherein R^{13} is R^{20}O or $\text{R}^{20}\text{R}^{21}\text{N}$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, ($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_6\text{-}\text{C}_{10}$)aryl($\text{C}_1\text{-}\text{C}_6$)alkyl or ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkyl; or $\text{R}^{14}(\text{C}_1\text{-}\text{C}_6)$ alkyl wherein R^{14} is $(\text{C}_1\text{-}\text{C}_6)\text{acylpiperazino}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylpiperazino}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}(\text{C}_1\text{-}\text{C}_6)\text{acylpiperazino}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperazino}$, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, $(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperidyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylpiperidyl}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}(\text{C}_1\text{-}\text{C}_6)\text{acylpiperidyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperidyl}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperidyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxyacyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylaminoaryl}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{aminoacyl}$ or $(\text{C}_1\text{-}\text{C}_6)\text{acylpiperidyl}$;
- R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, ($\text{C}_1\text{-}\text{C}_6$)alkyl, amino, hydroxy, ($\text{C}_1\text{-}\text{C}_6$)alkoxy, ($\text{C}_1\text{-}\text{C}_6$)alkylamino, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})\text{amino}$, ($\text{C}_1\text{-}\text{C}_6$)acylamino, ($\text{C}_1\text{-}\text{C}_6$)acyl($\text{C}_1\text{-}\text{C}_6$)alkylamino, carboxy, ($\text{C}_1\text{-}\text{C}_6$)alkoxyacyl, ($\text{C}_1\text{-}\text{C}_6$)alkylaminoacyl, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{aminoacyl}$, aminoacyl, trifluoromethyl, trifluoromethyl($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)alkyl (difluoromethylene), ($\text{C}_1\text{-}\text{C}_3$)alkyl(difluoromethylene)($\text{C}_1\text{-}\text{C}_3$)alkyl, ($\text{C}_6\text{-}\text{C}_{10}$)aryl, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl, ($\text{C}_6\text{-}\text{C}_{10}$)aryl($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_6\text{-}\text{C}_{10})\text{aryl}$, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_6\text{-}\text{C}_{10})\text{alkyl}$, ($\text{C}_3\text{-}\text{C}_6$)cycloalkyl, ($\text{C}_3\text{-}\text{C}_6$)cycloalkyl($\text{C}_1\text{-}\text{C}_6$)alkyl, hydroxy($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)acyloxy($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)alkoxy($\text{C}_1\text{-}\text{C}_6$)alkyl, piperazinyl($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)acylamino($\text{C}_1\text{-}\text{C}_6$)alkyl, piperidyl, ($\text{C}_1\text{-}\text{C}_6$)alkylpiperidyl, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkoxy($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)alkylthio($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_6\text{-}\text{C}_{10})\text{arylsulfinyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, ($\text{C}_1\text{-}\text{C}_6$)alkylsulfonyl($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_6\text{-}\text{C}_{10})\text{arylsulfonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, amino($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_1\text{-}\text{C}_6$)alkylamino($\text{C}_1\text{-}\text{C}_6$)alkyl, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $\text{R}^{13}\text{CO}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ or $\text{R}^{13}\text{CO}(\text{C}_3\text{-}\text{C}_{10})\text{cycloalkyl}$ wherein R^{13} is R^{20}O or $\text{R}^{20}\text{R}^{21}\text{N}$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, ($\text{C}_1\text{-}\text{C}_6$)alkyl, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ or ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkyl; R^{14} , $\text{R}^{14}(\text{C}_1\text{-}\text{C}_6)$ alkyl or $\text{R}^{14}(\text{C}_3\text{-}\text{C}_{10})\text{cycloalkyl}$ wherein R^{14} is ($\text{C}_1\text{-}\text{C}_6$)acylpiperazino, ($\text{C}_6\text{-}\text{C}_{10})\text{arylpiperazino}$, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)acylpiperazino, ($\text{C}_1\text{-}\text{C}_6$)alkylpiperazino, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperazino}$, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, ($\text{C}_1\text{-}\text{C}_6$)alkylpiperidyl, ($\text{C}_6\text{-}\text{C}_{10})\text{arylpiperidyl}$, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkylpiperidyl, ($\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperidyl}$, ($\text{C}_5\text{-}\text{C}_9$)heteroaryl($\text{C}_1\text{-}\text{C}_6$)alkylpiperidyl or ($\text{C}_1\text{-}\text{C}_6$)acylpiperidyl; or a group of the formula



5 wherein p is 0, 1, 2 or 3; and

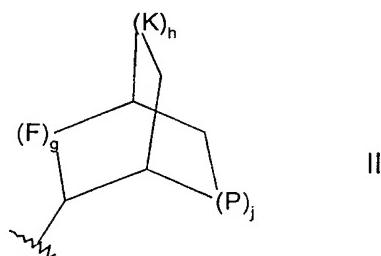
Z is hydroxy, (C_1 - C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1 - C_6)alkyl, piperidyl, (C_1 - C_6)alkylpiperidyl, (C_6 - C_{10})arylpiperidyl, (C_5 - C_9)heteroaryl(C_1 - C_6)alkylpiperidyl, (C_6 - C_{10})aryl(C_1 - C_6)alkylpiperidyl, (C_5 - C_9)heteroaryl(C_1 - C_6)alkylpiperidyl, (C_1 - C_6)acylpiperidyl, (C_6 - C_{10})aryl, (C_5 - C_9)heteroaryl, (C_6 - C_{10})aryl(C_1 - C_6)alkyl, (C_5 - C_9)heteroaryl(C_1 - C_6)alkyl, (C_6 - C_{10})aryl(C_6 - C_{10})aryl, (C_6 - C_{10})aryl(C_6 - C_{10})aryl(C_1 - C_6)alkyl, (C_3 - C_6)cycloalkyl, (C_3 - C_6)cycloalkyl(C_1 - C_6)alkyl, R^5 (C_1 - C_6)alkyl, (C_1 - C_6)alkyl(CHR^5)(C_1 - C_6)alkyl wherein R^5 is hydroxy, (C_1 - C_6)acyloxy, (C_1 - C_6)alkoxy, piperazino, (C_1 - C_6)acylamino, (C_1 - C_6)alkylthio, (C_6 - C_{10})arylthio, (C_1 - C_6)alkylsulfinyl, (C_6 - C_{10})arylssulfanyl, (C_1 - C_6)alkylsulfoxyl, (C_6 - C_{10})arylssulfoxyl, amino, (C_1 - C_6)alkylamino, ((C_1 - C_6)alkyl)₂ amino, (C_1 - C_6)acylpiperazino, (C_1 - C_6)alkylpiperazino, (C_6 - C_{10})aryl(C_1 - C_6)alkylpiperazino, (C_5 - C_9)heteroaryl(C_1 - C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R^6 (C_1 - C_6)alkyl, (C_1 - C_5)alkyl(CHR^6)(C_1 - C_6)alkyl wherein R^6 is piperidyl, (C_1 - C_6)alkylpiperidyl, (C_6 - C_{10})arylpiperidyl, (C_6 - C_{10})aryl(C_1 - C_6)alkylpiperidyl, (C_5 - C_9)heteroaryl(C_1 - C_6)alkylpiperidyl; or (C_5 - C_9)heteroaryl(C_1 - C_6)alkylpiperidyl;

20 or R^1 is defined as OR^9 or $S(O)_qR^9$ wherein q is 0, 1 or 2; and

R^9 is selected from the group consisting of trifluoromethyl(C_1 - C_6)alkyl, (C_1 - C_3)alkyl(difluoromethylene)(C_1 - C_3)alkyl, (C_3 - C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, hydroxy, (C_1 - C_6) alkoxy, halo, (C_1 - C_6)alkyl $S(O)_m$ wherein m is 0, 1 or 2; $R^{15}R^{16}NS(O)_m$ wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1 - C_6)alkyl; (C_1 - C_6)acyl, (C_1 - C_6)alkylamino, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy-CO-NH, (C_1 - C_6)alkylamino-CO-, $R^{15}R^{16}N$ -CO-O-, $R^{15}R^{16}N$ -CO-(C_1 - C_6)alkyl wherein R^{15} and R^{16} are as defined above; (C_2 - C_6)alkenyl, (C_2 - C_6) alkynyl, (C_1 - C_6)alkylamino, amino(C_1 - C_6)alkyl, hydroxy(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy(C_1 - C_6)alkyl, (C_1 - C_6)acyloxy(C_1 - C_6)alkyl, nitro, cyano(C_1 - C_6)alkyl, nitro(C_1 - C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1 - C_6)alkyl, (C_1 - C_6)acylamino, (C_1 - C_6)alkoxy(C_1 - C_6)acylamino, amino(C_1 - C_6)acyl, (C_1 - C_6)alkylamino(C_1 - C_6)acyl or ((C_1 - C_6)alkyl)₂ amino(C_1 - C_6)acyl; (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_3 - C_{10})cycloalkyl(C_1 - C_6)alkyl, (C_1 - C_6)acyloxy(C_1 - C_6)alkyl, (C_2 - C_6)alkoxy(C_1 - C_6)alkyl, piperazinyl(C_1 - C_6)alkyl, (C_1 - C_6)acylamino(C_1 - C_6)alkyl, (C_6 - C_{10})aryl(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, (C_5 - C_9)heteroaryl(C_1 - C_6)alkoxy(C_1 - C_6)alkyl, (C_1 - C_6)alkylthio(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfinyl(C_1 - C_6)alkyl, (C_6 - C_{10})arylssulfanyl(C_1 - C_6)alkyl, (C_1 - C_6)alkylsulfonyl(C_1 - C_6)alkyl, (C_6 - C_{10})arylssulfonyl(C_1 - C_6)alkyl, amino(C_1 - C_6)alkyl, (C_1 - C_6)alkylamino(C_1 - C_6)alkyl, ((C_1 - C_6)alkyl)₂ amino, (C_1 - C_6)alkyl wherein the alkyl group is optionally substituted by one to five cyano, nitro, hydroxy, carboxy, (C_1 - C_6)acylamino, (C_1 - C_6)alkoxy(C_1 - C_6)acylamino, amino(C_1 - C_6)acyl, (C_1 - C_6)alkylamino(C_1 - C_6)acyl or ((C_1 - C_6)alkyl)₂ amino(C_1 - C_6)acyl; $R^{13}CO(C_1$ - $C_6)$)alkyl or $R^{13}CO(C_3$ - C_{10})cycloalkyl wherein R^{13} is $R^{20}C$

- 5 or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, $(C_1-C_6)alkyl$, $(C_6-C_{10})aryl(C_1-C_6)alkyl$ or $(C_5-C_9)heteroaryl(C_1-C_6)alkyl$; R^{14} , $R^{14}(C_1-C_6)alkyl$ or $R^{14}(C_3-C_{10})cycloalkyl$ wherein R^{14} is $(C_2-C_9)heterocycloalkyl$, $(C_1-C_6)acylpiperazino$, $(C_6-C_{10})arylpiperazino$, $(C_5-C_9)heteroarylpiperazino$, $(C_1-C_6)alkylpiperazino$, $(C_6-C_{10})aryl(C_1-C_6)alkylpiperazino$, $(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino$, morpholino, thiomorpholino, 10 piperidino, pyrrolidino, piperidyl, $(C_1-C_6)alkylpiperidinyl$, $(C_6-C_{10})arylpiperidyl$, $(C_5-C_9)heteroarylpiperidyl$, $(C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl$, $(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl$ or $(C_1-C_6)acylpiperidyl$;

or R^9 is a group of the formula



- 15 wherein g, h and j are each independently 0 to 6;

F , K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8 wherein R^6 , R^7 and R^8 are as defined above;

- 15 R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, $(C_2-C_6)alkenyl$, $(C_2-C_6)alkynyl$, trifluoromethyl, trifluoromethoxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$ wherein the alkyl or alkoxy groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6)alkylthio, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$, $(C_3-C_9)cycloalkyl$ or $(C_6-C_{10})aryl$; or R^2 and R^3 are each independently $(C_3-C_{10})cycloalkyl$, $(C_3-C_{10})cycloalkoxy$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, $(C_6-C_{10})arylamino$, $(C_1-C_6)alkylthio$, $(C_6-C_{10})arylthio$, $(C_1-C_6)alkylsulfinyl$, $(C_6-C_{10})arylsulfinyl$, $(C_1-C_6)alkylsulfonyl$, $(C_6-C_{10})arylsulfonyl$, $(C_1-C_6)acyl$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkylamino-CO-$, $(C_5-C_9)heteroaryl$, $(C_2-C_9)heterocycloalkyl$ or $(C_6-C_{10})aryl$ wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-CO-NH-$, $(C_1-C_6)alkoxy-CO-NH-$, $(C_1-C_6)alkyl-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy-CO-NH-(C_1-C_6)alkoxy$, carboxy, carboxy(C_1-C_6)alkyl, carboxy(C_1-C_6)alkoxy, benzyloxycarbonyl(C_1-C_6)alkoxy, $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkoxy$, $(C_6-C_{10})aryl$, amino, amino(C_1-C_6)alkyl, $(C_1-C_6)alkoxycarbonylamino$, $(C_6-C_{10})aryl(C_1-C_6)alkoxycarbonylamino$, $(C_1-C_6)alkylamino$, $((C_1-C_6)alkyl)_2amino$, $(C_1-C_6)alkylamino(C_1-C_6)alkyl$, $((C_1-C_6)alkyl)_2amino(C_1-C_6)alkyl$, hydroxy, $(C_1-C_6)alkoxy$, carboxy, carboxy(C_1-C_6)alkyl;

- 5 (C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkoxycarbonyl(C_1-C_6)alkyl, (C_1-C_6) alkoxy-CO-NH-,
 (C_1-C_6) alkyl-CO-NH-, cyano, (C_5-C_9) heterocycloalkyl, amino-CO-NH-, (C_1-C_6) alkylamino-CO-NH-,
 $((C_1-C_6)$ alkyl)₂amino-CO-NH-, (C_6-C_{10}) arylamino-CO-NH-, (C_5-C_9) heteroaryl-amino-CO-NH-,
 (C_1-C_6) alkylamino-CO-NH-(C_1-C_6)alkyl, $((C_1-C_6)$ alkyl)₂amino-CO-NH-(C_1-C_6)alkyl, (C_6-C_{10}) arylamino-CO-NH-(C_1-C_6)alkyl, (C_5-C_9) heteroaryl-amino-CO-NH-(C_1-C_6)alkyl, (C_1-C_6) alkylsulfonyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino(C_1-C_6)alkyl, (C_6-C_{10}) arylsulfonyl, (C_6-C_{10}) arylsulfonylamino, (C_6-C_{10}) arylsulfonylamino(C_1-C_6)alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino(C_1-C_6)alkyl, (C_5-C_9) heteroaryl or (C_2-C_9) heterocycloalkyl;
- 10 with the proviso that when either R⁴ and R⁵ is hydrogen, the other of R⁴ or R⁵ cannot
15 be (C_6-C_{10}) aryl or (C_6-C_{10}) aryl(C_1-C_6)alkyl;
- with the proviso that when R⁴ is hydrogen, unsubstituted (C_1-C_6) alkyl or unsubstituted
 (C_3-C_{10}) cycloalkyl, R⁵ cannot be (C_6-C_{10}) aryl(C_1-C_6)alkyl; R²⁰ and R²¹ cannot be (C_5-C_9) heteroaryl(C_1-C_6)alkyl; and R¹⁴ cannot be (C_2-C_9) heterocycloalkyl, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidinyl or (C_1-C_6) alkylpiperidinyl;
- 20 with the proviso that the sp² and sp carbons of alkenyl or alkynyl cannot be substituted by hydroxy or amino;
- with the proviso that when R⁴ is hydrogen, R⁵ cannot be amino (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_1-C_6) alkylamino(C_1-C_6)alkyl, $((C_1-C_6)$ alkyl)₂amino(C_1-C_6)alkyl, furanyl, (C_1-C_6) alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl;
- 25 with the proviso that both R⁴ and R⁵ cannot both be hydroxy (C_1-C_6) alkyl;
- with the proviso that when R⁴ is (C_1-C_6) alkyl, R⁵ cannot be (C_1-C_6) alkoxy(C_1-C_6)alkyl or carboxy(C_1-C_6)alkyl; and
- with the proviso that R¹ cannot be carboxy(C_1-C_6)alkylthio or (C_1-C_6) alkoxycarbonyl(C_1-C_6)alkylthio.
- 30 The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.
- 35 The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those

5 compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower 10 alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

15 The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

20 The compounds of this invention may contain double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

25 Unless otherwise indicated, the alkyl and alkenyl groups referred to herein, as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched, and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl) or be linear or branched and contain cyclic moieties. Unless otherwise indicated, halogen includes fluorine, chlorine, bromine, and iodine.

(C₃-C₁₀)Cycloalkyl when used herein refers to cycloalkyl groups containing zero to two levels of unsaturation such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, 1,3-cyclohexadiene, cycloheptyl, cycloheptenyl, bicyclo[3.2.1]octane, norbornanyl etc..

30 (C₂-C₉)Heterocycloalkyl when used herein refers to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranlyl, tetrahydropyranyl, pyranyl, thiopyranyl, aziridinyl, oxiranyl, methylenedioxyl, chromenyl, isoxazolidinyl, 1,3-oxazolidin-3-yl, isothiazolidinyl, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,3-pyrazolidin-1-yl, piperidinyl, thiomorpholinyl, 1,2-tetrahydrothiazin-2-yl, 1,3-tetrahydrothiazin-3-yl, tetrahydrothiadiazinyl, morpholinyl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, tetrahydroazepinyl, piperazinyl, chromanyl, etc. One of ordinary skill in 35 the art will understand that the connection of said (C₂-C₉)heterocycloalkyl rings is through a carbon or a sp³ hybridized nitrogen heteroatom.

(C₂-C₉)Heteraryl when used herein refers to furyl, thienyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl,

5 pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthetyl, isothianaphthetyl, benzofuranyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, 10 benzoxazinyl; etc. One of ordinary skill in the art will understand that the connection of said (C_2-C_9)heterocycloalkyl rings is through a carbon atom or a sp^3 hybridized nitrogen heteroatom. (C_6-C_{10})aryl when used herein refers to phenyl or naphthyl.

Compounds of formula (I) may be administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents. These agents may include but are not limited to cyclosporin A (e.g. Sandimmune[®] or Neoral[®]), rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept[®]), azathioprine (e.g. Imuran[®]), daclizumab (e.g. Zenapax[®]), OKT3 (e.g. Orthoclone[®]), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, 20 piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone). These agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

The compounds of this invention include all conformational isomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., enantiomers and 25 diastereomers), as well as racemic, diastereomeric and other mixtures of such isomers.

Preferred compounds of formula I include those wherein R^1 is NR^4R^5 .

Other preferred compounds of formula I include those wherein R^4 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by hydroxy, amino, trifluoromethyl, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, 30 ((C_1-C_6)alkyl)₂amino or (C_1-C_6)acylamino; or R^4 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by hydroxy, trifluoromethyl or (C_1-C_6)acyloxy.

Other preferred compounds of formula I include those wherein R^5 is (C_3-C_{10})cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five deuterium, hydroxy, trifluoromethyl, halo, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyl, (C_1-C_6)alkylamino(C_1-C_6)acyl, ((C_1-C_6)alkyl)₂amino(C_1-C_6)acyl, (C_1-C_6)acylamino, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, halo(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, $R^{15}S(O)_m R^{16}N$, $R^{15}S(O)_m R^{16}N(C_1-C_6)$ alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl.

Other preferred compounds of formula I include those wherein R^2 and R^3 are each 40 independently selected from the group consisting of hydrogen, halo, (C_1-C_6)alkyl, (C_2-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)acyl, (C_1-C_6)acyloxy, (C_1-C_6)alkylamino, (C_1-C_6)acylamino, (C_1-C_6)alkoxy-CO-NH, (C_1-C_6)alkylamino-CO-, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, halo(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, $R^{15}S(O)_m R^{16}N$, $R^{15}S(O)_m R^{16}N(C_1-C_6)$ alkyl wherein m is 0, 1 or 2 and R^{15} and R^{16} are each independently selected from hydrogen or (C_1-C_6)alkyl.

5 C_6)alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkoxy, (C_3-C_{10}) cycloalkyl, (C_3-C_{10}) cycloalkoxy, (C_2-C_9) heterocycloalkyl, (C_5-C_9) heteroaryl or (C_6-C_{10}) aryl.

Specific preferred compounds of formula I include the following:

- 2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexyl}-propan-2-ol;
- 10 2-{3-[(2-Hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-4-methyl-cyclohexyl}-propan-2-ol;
- 15 2-[(5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
- 15 (5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amine;
- 20 2-{4-Methyl-3-[(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amino]-cyclohexyl}-propan-2-ol;
- 20 2-{4-Methyl-5-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohex-3-enyl}-propan-2-ol;
- 20 2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-3-yl]-propan-2-ol;
- 20 2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-2-yl]-propan-2-ol;
- 20 (5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(5-isopropenyl-2-methyl-cyclohexyl)-methyl-amine;
- 25 2-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-cyclohexyl}-propan-2-ol;
- 25 (2-Ethyl-4-isopropenyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- 25 2-{3-Ethyl-4-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol;
- 25 2-{3-Ethyl-4-[(2-hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol;
- 30 2-[(2-Ethyl-4-isopropenyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
- 30 (5-(S)-Isopropenyl-2-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
- 30 3-Methyl-8-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-8-aza-bicyclo[3.2.1]octan-3-ol;
- 35 2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
- 35 2-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
- 35 Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine; and
- 35 4-Piperidin-1-yl-5-m-tolyl-7H-pyrrolo[2,3-d]pyrimidine.
- The present invention also relates to a pharmaceutical composition for (a) treating or
40 preventing a disorder or condition selected from organ transplant rejection, lupus, multiple

5 sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

The present invention also relates to a pharmaceutical composition for (a) treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases or (b) the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents, effective in such disorders or conditions and a pharmaceutically acceptable carrier.

20 The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

25 The present invention also relates to a method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents.

The present invention also relates to a method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, Leukemia, and other autoimmune diseases in a mammal, including a human,

-12-

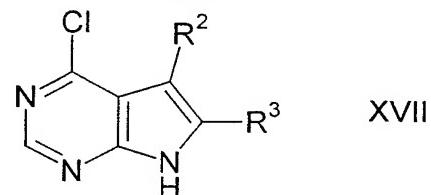
- 5 comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof, alone or in combination with T-cell immunosuppressant or antiinflammatory agents, effective in treating such a condition.

-13-

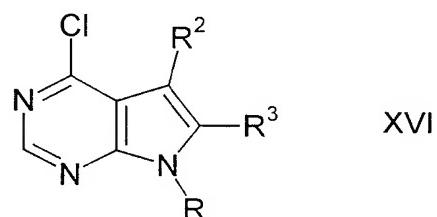
5

Detailed Description of the Invention

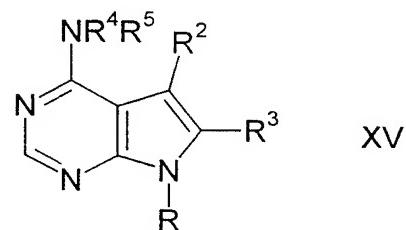
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R¹, R², R³ and R⁹ in the reaction Schemes and the discussion that follow are defined as above.

SCHEME 1

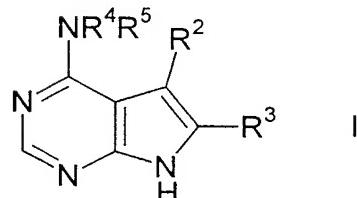
↓ 1



↓ 2



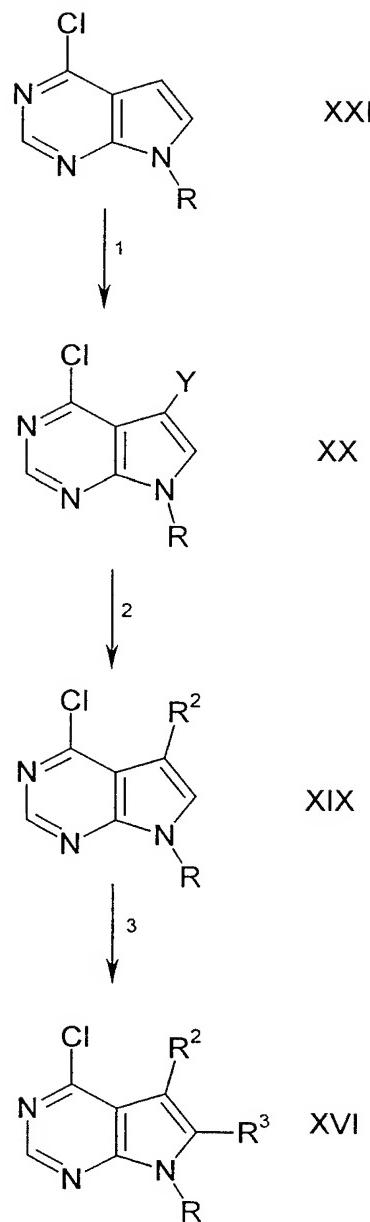
↓ 3



10

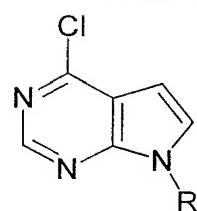
-14-

5

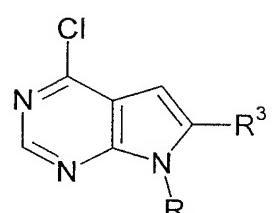
SCHEME 2

-15-

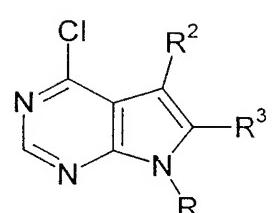
5

SCHEME 3

XXI

↓
1

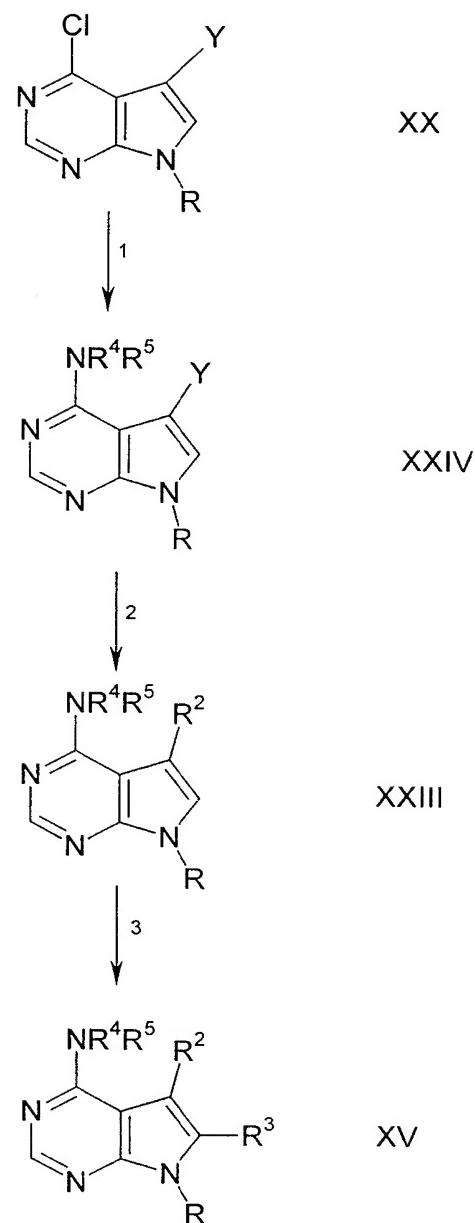
XXII

↓
2

XVI

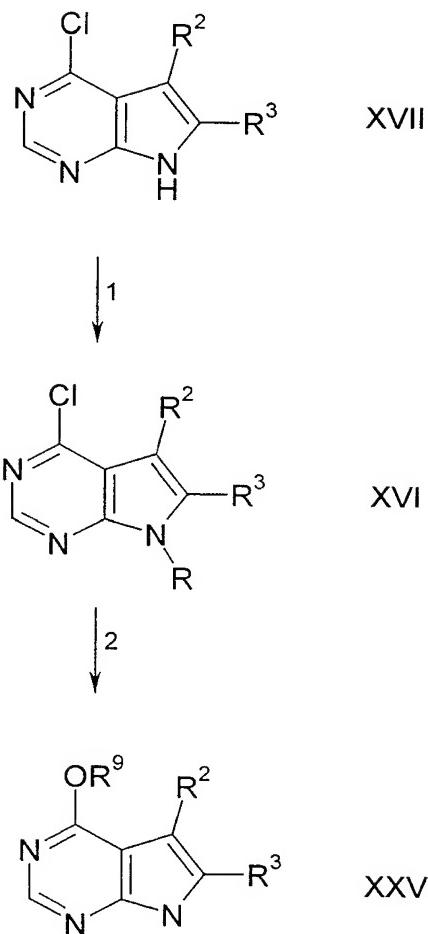
-16-

5

SCHEME 4

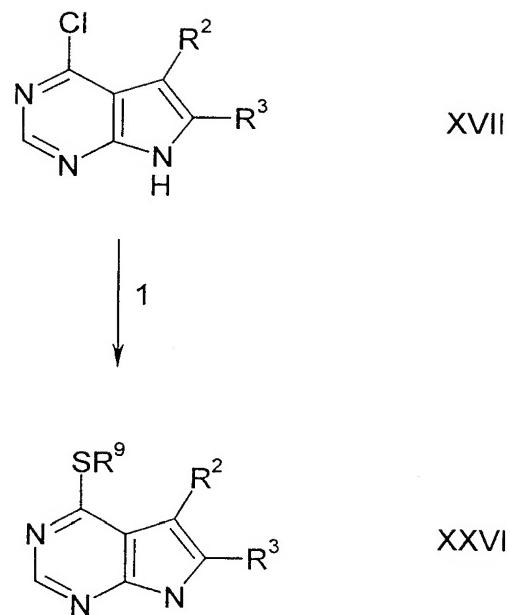
-17-

5

SCHEME 5

-18-

5

SCHEME 6

5 In reaction 1 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVII is converted to the corresponding compound of formula XVI, wherein R is benzenesulfonyl or benzyl, by treating XVII with benzenesulfonyl chloride, benzylchloride or benzylbromide in the presence of a base, such as sodium hydride or potassium carbonate, and a polar aprotic solvent, such as dimethylformamide or tetrahydrofuran. The reaction
10 mixture is stirred at a temperature between about 0°C to about 70°C, preferably about 30°C, for a time period between about 1 hour to about 3 hours, preferably about 2 hours.

In reaction 2 of Scheme 1, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XVI is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula XV by coupling XVI with an amine of the formula HNR⁴R⁵. The reaction is carried out in an
15 alcohol solvent, such as tert-butanol, methanol or ethanol, or other high boiling organic solvents, such as dimethylformamide, 1,4-dioxane or 1,2-dichloroethane, at a temperature between about 60°C to about 120°C, preferably about 80°C. Typical reaction times are between about 2 hours to about 48 hours, preferably about 16 hours.

20 In reaction 3 of Scheme 1, removal of the protecting group from the compound of formula XV, wherein R is benzenesulfonyl, to give the corresponding compound of formula I, is carried out by treating XV with an alkali base, such as sodium hydroxide or potassium hydroxide, in an alcohol solvent, such as methanol or ethanol, or mixed solvents, such as alcohol/tetrahydrofuran or alcohol/water. The reaction is carried out at room temperature for a time period between about 15 minutes to about 1 hour, preferably 30 minutes. Removal of the
25 protecting group from the compound of formula XV, wherein R is benzyl, is conducted by treating XV with sodium in ammonia at a temperature of about -78°C for a time period between about 15 minutes to about 1 hour.

In reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula XXI, wherein R is hydrogen or benzenesulfonate, is converted to the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula XX, wherein Y is chloro, bromo or iodo, by reacting XXI with N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide. The reaction mixture is heated to reflux, in chloroform, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, in reaction 1 of Scheme 2, the 4-chloropyrrolo[2,3-d]pyrimidine of formula XXI, wherein R is hydrogen, is converted to the
35 corresponding 4-chloro-5-nitropyrrolo[2,3-d]pyrimidine of formula XX, wherein Y is nitro, by reacting XXI with nitric acid in sulfuric acid at a temperature between about -10°C to about 10°C, preferably about 0°C, for a time period between about 5 minutes to about 15 minutes, preferably about 10 minutes. The compound of formula XXI, wherein Y is nitro, is converted to the corresponding 4-chloro-5-aminopyrrolo[2,3-d]pyrimidine of the formula XX, wherein Y is

5 amino, by reacting **XXI** under a variety of conditions known to one skilled in the art such as palladium hydrogenolysis or tin(IV)chloride and hydrochloric acid.

In reaction 2 of Scheme 2, the 4-chloro-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XX**, wherein R is hydrogen, is converted to the corresponding compound of formula **XIX**, wherein R² is (C₁-C₆)alkyl or benzyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, and reacting the dianion intermediate so formed with an alkylhalide or benzylhalide at a temperature between about -78°C to room temperature, preferably room temperature. Alternatively, the dianion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-5-hydroxypyrrrolo[2,3-d]pyrimidine compound of formula **XIX**, wherein R² is hydroxy. The compound of formula **XX**, wherein Y is bromine or iodine and R is benzenesulfonate, is converted to the compound of formula **XIX**, wherein R² is (C₆-C₁₂)aryl or vinyl, by treating **XX** with N-butyllithium, at a temperature of about -78°C, followed by the addition of zinc chloride, at a temperature of about -78°C. The corresponding organo zinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The reaction mixture is stirred at a temperature between about 20 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour.

In reaction 3 of Scheme 2, the compound of formula **XIX** is converted to the corresponding compound of formula **XVI** by treating **XIX** with N-butyllithium, lithium diisopropylamine or sodium hydride, at a temperature of about -78°C, in the presence of a polar aprotic solvent, such as tetrahydrofuran. The anionic intermediate so formed is further reacted with (a) alkylhalide or benzylhalide, at a temperature between about -78°C to room temperature, preferably -78 °C, when R³ is alkyl or benzyl; (b) an aldehyde or ketone, at a temperature between about -78°C to room temperature, preferably -78°C, when R³ is alkoxy; and (c) zinc chloride, at a temperature between about -78°C to room temperature, preferably -78°C, and the corresponding organozinc intermediate so formed is then reacted with aryl iodide or vinyl iodide in the presence of a catalytic quantity of palladium. The resulting reaction mixture is stirred at a temperature between about 50°C to about 80°C, preferably about 70°C, for a time period between about 1 hour to about 3 hours, preferably about 1 hour. Alternatively, the anion so formed is reacted with molecular oxygen to form the corresponding 4-chloro-6-hydroxypyrrrolo[2,3-d]pyrimidine compound of formula **XVI**, wherein R³ is hydroxy.

In reaction 1 of Scheme 3, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XXI** is converted to the corresponding compound of formula **XXII**, according to the procedure described above in reaction 3 of Scheme 2.

5 In reaction 2 of Scheme 3, the compound of formula **XXII** is converted to the corresponding compound of formula **XVI**, according to the procedures described above in reactions 1 and 2 of Scheme 3.

10 In reaction 1 of Scheme 4, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XX** is converted to the corresponding 4-aminopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, according to the procedure described above in reaction 2 of Scheme 1.

15 In reaction 2 of Scheme 4, the 4-amino-5-halopyrrolo[2,3-d]pyrimidine compound of formula **XXIV**, wherein R is benzenesulfonate and Z is bromine or iodine, is converted to the corresponding compound of formula **XXIII** by reacting **XXIV** with (a) arylboronic acid, when R² is aryl, in an aprotic solvent, such tetrahydrofuran or dioxane, in the presence of a catalytic quantity of palladium (0) at a temperature between about 50°C to about 100°C, preferably about 70°C, for a time period between about 2 hours to about 48 hours, preferably about 12 hours; (b) alkynes, when R² is alkynyl, in the presence of a catalytic quantity of copper (I) iodide and palladium (0), and a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 1 hour to about 5 hours, preferably about 3 hours; and (c) alkenes or styrenes, when R² is vinyl or styrenyl, in the presence of a catalytic quantity of palladium in dimethylformamide, dioxane or tetrahydrofuran, at a temperature between about 80°C to about 100°C, preferably about 100°C, for a time period between about 2 hours to about 48 hours, preferably about 48 hours.

20 In reaction 3 of Scheme 4, the compound of formula **XXIII** is converted to the corresponding compound of formula **XV**, according to the procedure described above in reaction 3 of Scheme 2.

25 In reaction 1 of Scheme 5, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XVI**, wherein R is defined as above, according to the procedure described above in reaction 1 of Scheme 1.

30 In reaction 2 of Scheme 5, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVI** is converted to the corresponding compound of formula **XXV** by coupling **XVI** with a compound of the formula, R⁹OH, in the presence of sodium hydroxide. The reaction is carried out in a polar aprotic solvent, such as tetrahydrofuran, and heated to reflux for a time period between about 2 hours to about 4 hours, preferably about 3 hours. Removal of the protecting group is carried out according to the procedure described above in reaction 3 of Scheme 1.

35 In reaction 1 of Scheme 6, the 4-chloropyrrolo[2,3-d]pyrimidine compound of formula **XVII** is converted to the corresponding compound of formula **XXVI** by coupling **XVII** with a compound of the formula, SR⁹, in the presence of potassium tert-butoxide and a polar aprotic solvent, such as tetrahydrofuran. The resulting reaction mixture is heated to reflux for a time period between about 2.5 hours to about 5 hours, preferably about 3.5 hours. The compound

5 of formula **XXVI** may be further reacted with an oxidizing agent known to one of ordinary skill in the art, such as hydrogen peroxide, oxone, 3-chloroperoxybenzoic acid or tert-butylperoxide to generate the corresponding 4- R⁹ sulfinylpyrrolo[2,3-d]pyrimidine or 4- R⁹ sulfonylpyrrolo compounds.

10 The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter 15 free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can 20 also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the present invention that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium 25 salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating 30 the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, 35 stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, 40 intramuscular or subcutaneous) or rectal administration or in a form suitable for administration

- 5 by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, 10 polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or 15 suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or 25 infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., 30 sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of 35 the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be 40 determined by providing a valve to deliver a metered amount. The pressurized container or

5 nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

10 A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

15 Aerosol formulations for treatment of the conditions referred to above (e.g., asthma) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose with an aerosol will be within the range 0.1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

20 A compound of formula (I) administered in a pharmaceutically acceptable form either alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, agents which may include but are not limited to cyclosporin A (e.g. Sandimmune[®] or Neoral[®], rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (e.g. Cellcept[®]), azathioprine (e.g. Imuran[®]), daclizumab (e.g. Zenapax[®]), OKT3 (e.g. Orthocolone[®]), AtGam, aspirin, acetaminophen, ibuprofen, naproxen, 25 piroxicam, and antiinflammatory steroids (e.g. prednisolone or dexamethasone); and such agents may be administered as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice.

FK506 (Tacrolimus) is given orally at 0.10-0.15 mg/kg body weight, every 12 hours, within first 48 hours postoperative. Dose is monitored by serum Tacrolimus trough levels.

30 Cyclosporin A (Sandimmune oral or intravenous formulation, or Neoral[®], oral solution or capsules) is given orally at 5 mg/kg body weight, every 12 hours within 48 hours postoperative. Dose is monitored by blood Cyclosporin A trough levels.

35 The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397.

The ability of the compounds of formula I or their pharmaceutically acceptable salts to inhibit Janus Kinase 3 and, consequently, demonstrate their effectiveness for treating disorders or conditions characterized by Janus Kinase 3 is shown by the following in vitro assay tests.

5

Biological AssayJAK3 (JH1:GST) Enzymatic Assay

The JAK3 kinase assay utilizes a protein expressed in baculovirus-infected SF9 cells (a fusion protein of GST and the catalytic domain of human JAK3) purified by affinity chromatography on glutathione-Sepharose. The substrate for the reaction is poly-Glutamic acid-Tyrosine (PGT (4:1), Sigma catalog # P0275), coated onto Nunc Maxi Sorp plates at 100 µg/ml overnight at 37°C. The morning after coating, the plates are washed three times and JAK3 is added to the wells containing 100 µl of kinase buffer (50 mM HEPES, pH 7.3, 125 mM NaCl, 24 mM MgCl₂) + 0.2 uM ATP + 1 mM Na orthovanadate.) The reaction proceeds for 30 minutes at room temperature and the plate is washed three more times. The level of phosphorylated tyrosine in a given well is quantitated by standard ELISA assay utilizing an anti-phosphotyrosine antibody (ICN PY20, cat. #69-151-1).

DND 39/IL-4 Cellular Assay for JAK3 kinase Inhibitors

The DND 39/IL-4 assay is designed to find inhibitors of JAK3 kinase activity which would be prime candidates for immunosuppressive and/or allergy. The assay uses a B-cell line called DND39 which has had the luciferase gene driven by the germ line IgE promoter stably integrated into one of the chromosomes. When these cells are stimulated with IL-4, the kinase JAK3, which is associated with the IL-4 receptor, phosphorylates the signal transducer STAT6. STAT6 then binds to the germline IgE promoter and starts transcription of the luciferase gene. Luciferase is measured in a lysate of these cells using the Promega luciferase assay reagent system.

Note: DND39 cells are grown in RPMI 1640 supplemented with 10% heat inactivated FCS, 2 mM L-Glutamine, and 100 units/ml Pen./Strep. The cells are maintained from 1x10⁵ to 1x10⁶ cells/ml. Split to 1x10⁵ on Friday, cells will be at about 1x10⁶ on Monday. Then split 1:2 during the week keeping 200 ml in a flask as needed.

30 3x10⁵ DND39 cells are plated in 100 µl of RPMI 1640 supplemented with 1% heat inactivated FCS, 2 mM L-glutamine, and 100 units/ml Pen/Step in a 96 well Vee bottom plate (Nunc). Compounds are diluted serially 1:2 in DMSO starting at 4mM to 1.9µM. In a 96 well polypropylene plate, changing tips after each dilution. Then 5µl of each dilution are added to 500µl of RPMI/1% serum in a 96 tube rack. 125 µL of the compound dilutions are added to the cells and incubated at 37°C, 5% CO₂ for one hour. After one hour, 25 µl of 25 ng/ml IL-4 is added to the cells and mixed. Final concentration of IL-4 is 2.5 ng/ml and final concentration of compound is from 20 µM to 156 nM. The cells are then incubated overnight 16-18 hours. The plate is then centrifuged at 2500-3000 RPM in a table top centrifuge for 5 minutes. The culture supernatant is carefully removed by aspiration with an 8 well maifold.
40 100 µl of PBS with calcium and magnesium is added to the pelleted cells. The cells are

5 resuspended in the PBS and transferred to a Packard white OptiPlate. 100 μ l of Packard's LucLite reagent is added to the wells of the OptiPlate.

The following Examples illustrate the preparation of the compounds of the present invention but it is not limited to the details thereof. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the 10 sample solvent (deuterochloroform unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 5989®, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which uses a 50/50 mixture 15 of acetonitrile/water with 0.1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C.

EXAMPLE 1

Cyclohexyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

METHOD A

20 Cyclohexyl-methyl-amine

To a solution of cyclohexanone (98 mg/1mmol) and acetic acid (120 mg/2 mmol) dissolved in 2.0 mL of 1,2-dichloroethane was added 2.0 mL of a 2 M solution of methylamine in methanol and the resulting mixture stirred at room temperature for 4 h. Polymer supported borohydride (1 g/2.5 mmol) was added and the mixture stirred at room temperature for 1 h 25 then filtered and concentrated to dryness in vacuo affording 66 mg (40%) of the title compound as the acetate salt. 1 H NMR (400 MHz)(CD₃OD) δ : 1.17 - 1.37 (m, 5H), 1.67 (br d, 1H, J = 12.5 Hz), 1.83 (br d, 2H, J = 18.7 Hz), 1.86 (s, 3H), 2.04 (br d, 2H, J = 10.2 Hz), 2.60 (s, 3H), 2.86 - 2.92 (m, 1H).

METHOD B

30 Cyclohexyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

A mixture of 200 mg (1.30 mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (prepared by the method of Davoll, J. Am. Chem. Soc., (1960), 82, 131), the product from Method A (589 mg/5.21 mmol) and 3 mL of tert-butanol was stirred in a sealed tube at 100 °C for 24 h. The reaction mixture was added to water, acidified to pH 1 with 1 N HCl (aq), washed twice 35 with diethylether (ether) and basified to pH 14 with 1 N sodium hydroxide (NaOH). The resulting precipitate was filtered and dried in vacuo to obtain 263 mg (88%) of the title compound, mp 177-180 °C. 1 H NMR (400 MHz, CDCl₃): δ 1.11-1.22 (m, 1H), 1.43-1.63 (m, 4H), 1.73 (br d, 1H, J = 13.3 Hz), 1.83-1.90 (m, 4 H), 3.23 (s, 3H), 4.69 (br, 1H), 6.53 (d, 1H, J = 3.5 Hz), 7.03 (d, 1H, J = 3.5 Hz), 8.30 (s, 1H), 10.6 (br, 1H). LRMS: 231 (M+1).

5 The title compounds of Examples 2-84 were prepared by a method analogous to that described in Example 1.

EXAMPLE 2

Benzyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Benzylethylamine. Melting Point: 170 - 172°C; LRMS: 252.3.

10

EXAMPLE 3

Methyl-(S)-1-phenyl-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(S)-1-phenylethylamine. Melting Point: 131°C; LRMS: 253.

15

EXAMPLE 4

Cyclopentyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclopentylmethylamine. LRMS: 217.3.

EXAMPLE 5

Allyl-cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Allylcyclohexylamine. LRMS: 257.

20

EXAMPLE 6

Allyl-cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Allylcyclopentylamine. Melting Point: 173 - 175°C; LRMS: 243.

25

EXAMPLE 7

Allyl-cyclopentyl 7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylethylamine. LRMS: 245.3.

EXAMPLE 8

(1-Cyclohexyl-ethyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Cyclohexylethyl)methylamine. LRMS: 259.4.

30

EXAMPLE 9

Cycloheptyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptylmethylamine. Melting Point: 177 - 178°C; LRMS: 245.3.

EXAMPLE 10

Cyclooctyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctylmethylamine. Melting Point: 188 - 189°C; LRMS: 259.4.

35

EXAMPLE 11

Methyl-(3-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(3-methylcyclohexyl)amine. LRMS: 245.3.

EXAMPLE 12

Methyl-(4-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(4-methylcyclohexyl)amine. LRMS: 245.3.

-28-

5

EXAMPLE 13

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(3,3,5-trimethyl-cyclohexyl)-amine

Methyl-(3,3,5-trimethylcyclohexyl)-amine. LRMS: 273.4.

10

EXAMPLE 14

Cycloheptyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptylethylamine. Melting Point: 168 - 169°C; LRMS: 259.4.

15

EXAMPLE 15

Cyclooctyl-ethyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctylethylamine. Melting Point: 155 - 156°C; LRMS: 273.4.

20

EXAMPLE 16

[1-(4-Chloro-phenyl)-propyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[1-(4-Chlorophenyl)-propyl]methylamine. LRMS: 301.7.

25

EXAMPLE 17

[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-methylamine. LRMS: 297.4.

30

EXAMPLE 18

(Decahydro-naphthalen-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Decahydronaphthalen-1-yl-methylamine. LRMS: 285.4.

35

EXAMPLE 19

Cyclodecyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclodecylmethylamine. LRMS: 287.1.

40

EXAMPLE 20

Cyclononyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclononylmethyl. LRMS: 273.1.

45

EXAMPLE 21

2-[Cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclopentylaminoethanol. Melting Point: 156 - 158°C; LRMS: 247.3.

50

EXAMPLE 22

Cycloheptyl-(2-methoxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptyl-(2-methoxy-ethyl)amine. LRMS: 289.

55

EXAMPLE 23

Cycloheptyl-cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cycloheptyl-cyclopropylamine. LRMS: 271.4.

-29-

5

EXAMPLE 24Cycloheptyl-cyclopropyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

Cyclohexylaminoethanol. Melt Point: 200 - 201°C; LRMS: 261.3.

10

EXAMPLE 25Cyclooctyl-(2-methoxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclooctyl-(2-methoxy-ethyl)amine. LRMS: 303.

15

EXAMPLE 26sec-Butyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

sec-Butyl-methylamine. Melting Point: 146 - 148°C; LRMS: 205.

20

EXAMPLE 272-[Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-1-phenyl-propan-1-ol

2-Methyl-1- phenyl-propan-1-ol. LRMS: 283, 265.

25

EXAMPLE 28[2-(4-Chloro-phenoxy)-1-methyl-ethyl]-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

[2-(4-Chlorophenoxy)-1-methylethyl]-methylamine. Melting Point: 139 - 141°C; LRMS: 319, 317, 189.

30

EXAMPLE 29N-Cyclohexyl-N',N'-dimethyl-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-propane-1,3-diamine

N-Cyclohexyl-N',N'-dimethyl propane-1,3-diamine. LRMS: 302.4.

35

EXAMPLE 30N-[2-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethyl]-acetamide

N-Cyclohexylaminoethyl acetamide. LRMS: 302.4. N-

40

EXAMPLE 312-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclohexylaminoethanol. Melting Point: 69 - 72°C; LRMS: 275.4.

EXAMPLE 322-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Cyclooctylaminethanol. Melting Point: 66 - 77°C; LRMS: 289.4.

EXAMPLE 33(3,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,5-Dimethylcyclohexyl)methylamine. LRMS: 259.4.

EXAMPLE 342-[Benzyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Benzylaminoethanol. LRMS: 269, 251.

-30-

5

EXAMPLE 35

3-[Cyclopentyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-1-ol

3-Cyclopentylamino-propan-1-ol. Melting Point: 162 - 164°C; LRMS: 261.3.

EXAMPLE 36

3-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-1-ol

10 3-Cycloheptylaminopropan-1-ol. Melting Point: 62 - 66°C; LRMS: 289.4.

EXAMPLE 37

2-[(Decahydro-naphthalen-2-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-Decahydronaphthalen-2-yl-aminoethanol. Melting Point: 75°C; LRMS: 315.

EXAMPLE 38

2-[(1-Ethyl-propyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-(1-Ethylpropyl)amine ethanol. Melting Point: 49 - 53°C; LRMS: 249.3.

EXAMPLE 39

1-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-butan-2-ol

Cyclohexylamino-butan-2-ol. LRMS: 289.

20

EXAMPLE 40

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2.1]hept-2-yl-methylamine. LRMS: 243.

EXAMPLE 41

2(S)-{[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-methyl}-cyclohexanol

2-(Cyclohexylamine)methylcyclohexanol. LRMS: 329.

25

EXAMPLE 42

2(R)-{[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-methyl}-cyclohexanol

30

2-(Cyclohexylamine)methylcyclohexanol. LRMS: 329.

EXAMPLE 43

(2-Ethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Ethylcyclopentyl)methyl amine. LRMS: 287.

EXAMPLE 44

35

Cyclononyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclononylmethylamine. LRMS: 273.

EXAMPLE 45

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,4,4-trimethyl-cyclopentyl)-amine

Methyl-2,4,4-trimethyl-cyclopentyl)-amine. LRMS: 259.

5

EXAMPLE 46(3-Ethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3-Ethyl-cyclopentyl)methylamine. LRMS: 245.

EXAMPLE 47(2,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

10 (2,5-Dimethylcyclohexyl)methyl-amine. LRMS: 259.

EXAMPLE 48(3,4-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,4-Dimethylcyclohexyl)methylamine. LRMS: 259.

15

(4-Isopropyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(4-Isopropylcyclohexyl)methylamine. LRMS: 273.

EXAMPLE 49(Decahydro-naphthalen-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(Decahydronaphthalen-1-yl)methylamine. LRMS: 285.

20

EXAMPLE 51(2,2-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,2-Dimethylcyclohexyl)methylamine. LRMS: 259.

25 amine

(2-Isopropyl-5-methylcyclohexyl)methylamine. LRMS: 287.

EXAMPLE 53Methyl-(3-methyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

30 Methyl-(3-methyl-cyclopentyl)amine. LRMS: 231.

35

EXAMPLE 54(1-Benzyl-piperidin-4-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(1-Benzylpiperidin-4-yl)methylamine. LRMS: 322.

35

EXAMPLE 55(4-tert-Butyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(4-tert-Butylcyclohexyl)methylamine. LRMS: 287.

35

EXAMPLE 56Indan-1-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Indan-1-yl-methylamine. LRMS: 265.

5

EXAMPLE 57

(4-Ethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine
 (4-Ethylcyclohexyl)methylamine. LRMS: 259.

10

EXAMPLE 58

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amine

15

Methyl-1,2,3,4-tetrahydro-naphthalen-2-yl-amine. LRMS: 279.

EXAMPLE 59

Bicyclo[3.2.1]oct-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine
 Bicyclo[3.2.1]oct-2-yl-methylamine. LRMS: 257.

20

EXAMPLE 60

Methyl-(octahydro-4,7-methano-inden-5-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(octahydro-4,7-methano-inden-5-yl)amine. LRMS: 283.

EXAMPLE 61

Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2.1]hept-2-yl-methylamine. LRMS: 243.

EXAMPLE 62

(5-Chloro-indan-1-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine
 (5-Chloro-indan-1-yl)methylamine. LRMS: 299.

25

EXAMPLE 63

Adamantan-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Adamantan-2-yl-methylamine. LRMS: 283.

EXAMPLE 64

(Decahydro-naphthalen-2-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

30

(Decahydro-naphthalen-2-yl)methylamine. LRMS: 285.

EXAMPLE 65

(3,5-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,5-Dimethylcyclohexyl)methylamine. LRMS: 259.

35

EXAMPLE 66

Bicyclo[3.3.1]non-9-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[3.3.1]non-9-yl-methylamine. LRMS: 271.

EXAMPLE 67

(1-Isopropyl-4-methyl-bicyclo[3.1.0]hex-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

40

(1-Isopropyl-4-methylbicyclo[3.1.0]hex-3-yl)-methylamine. LRMS: 285.

5

EXAMPLE 68Cyclobutyl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclobutylmethylamine. LRMS: 203.

10

EXAMPLE 69(2,2-Dimethyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,2-Dimethyl-cyclopentyl)methylamine. LRMS: 245.

15

EXAMPLE 704-[Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexanecarboxylic acidethyl ester

4-[Methylamino]cyclohexanecarboxylic acid. LRMS: 303.

20

EXAMPLE 71(2-Isopropyl-5-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Isopropyl-5-methyl-cyclohexyl)methylamine. LRMS: 287.

25

EXAMPLE 72(3,3-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(3,3-Dimethyl-cyclohexyl)methylamine. LRMS: 259.

30

EXAMPLE 731(S)-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-2-ol

1-[Cyclohexylamino]-propan-2-ol. LRMS: 275.4.

35

EXAMPLE 741(R)-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propan-2-ol

1-[Cyclohexylamino]-propan-2-ol. LRMS: 275.4.

40

EXAMPLE 753-[Cyclohexyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-propane-1,2-diol

3-[Cyclohexylamino]-propane-1,2-diol. LRMS: 291.4.

45

EXAMPLE 762-[(Decahydro-naphthalen-1-yl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol

2-[(Decahydro-naphthalen-1-yl)-amino]-ethanol. LRMS: 315.4.

EXAMPLE 772-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethyl}-carbamic acidtert-butyl ester

2-[(Cycloheptylamino)ethyl]carbamic acid. LRMS: 374.5.

-34-

5

EXAMPLE 78

Methyl-(3-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(3-methylcyclohexyl)amine. LRMS: 359.4.

10

EXAMPLE 79

Methyl-(2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(2-methylcyclohexyl)amine. LRMS: 359.4.

15

EXAMPLE 80

(2-Ethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2-Ethyl-cyclohexyl)methylamine. LRMS: 373.4.

20

EXAMPLE 81

Methyl-(2-propyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Methyl-(2-propylcyclohexyl)amine. LRMS: 387.4.

EXAMPLE 82

(2,4-Dimethyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

(2,4-Dimethylcyclohexyl)methylamine. LRMS: 373.4.

25

EXAMPLE 83

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,5,5-trimethyl-cyclohexyl)-amine

Methyl- (2,5,5-trimethylcyclohexyl)-amine. LRMS: 387.4.

EXAMPLE 84

Methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,5,5-tetramethyl-cyclohexyl)-amine

Methyl-(2,2,5,5-tetramethylcyclohexyl)-amine. LRMS: 401.

EXAMPLE 85

Cyclohexyl-methyl-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylmethylamine.

5

METHOD C7-Benzenesulfonyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

In a flame-dried flask under nitrogen, 780 mg of 60 % sodium hydride (19.5 mmol) in mineral oil was added to 30 mL of dimethylformamide (DMF) and the resulting mixture cooled to 0 °C. A solution of 2.0 g (13.0 mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine in 10 mL of 10 DMF was added slowly over a 5 min period. The reaction was stirred for 10 min at which time generation of hydrogen (H₂) ceased. Benzenesulfonylchloride (1.7 mL/13.0 mmol) was added, the reaction warmed to room temperature and stirred for 1 h. Water was added, and the resulting precipitate was filtered and dried in vacuo to obtain 3.4 g (89%) of the title compound as a crystalline solid, mp 163-167 °C.

15

METHOD D7-Benzenesulfonyl-4-chloro-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine

In a flame-dried flask under nitrogen, 0.53 mL (3.79 mmol) of diisopropylamine were dissolved in 5 mL of tetrahydrofuran (THF) and the solution cooled to -78 °C. n-Butyllithium (3.75 mmol as a 2.5 M solution in hexanes) was added and the resulting mixture brought to 0 20 °C with continued stirring for 10 min. The reaction mixture was again cooled to -78 °C and to this mixture added a solution of 1.0 g (3.40 mmol) of the product from Method C in 10 mL of THF over a 10 min period. The reaction mixture was stirred for 1 h at -78 °C, at which time, 8.2 mL (4.10 mmol) of a 0.5 M solution of zinc chloride in THF was added, the reaction mixture was brought to room temperature and stirred for 1 h. Iodobenzene (0.46 mL/4.11 25 mmol) and a suspension of 197 mg of tetrakis(triphenylphosphine) palladium in 2 mL of THF were added. The resulting mixture was stirred at reflux for 3 h., cooled to room temperature, and partitioned between dichloromethane and water. The aqueous layer was acidified with 1 N HCl and extracted twice with dichloromethane. The dichloromethane layers were combined, washed with 1 N HCl and brine, dried over magnesium sulfate (MgSO₄), filtered 30 and concentrated in vacuo to obtain the title compound. LRMS: 370, 372 (M+2).

METHOD E4-Chloro-6-phenyl-7H-pyrrolo[2,3-d]pyrimidine

The product from Method D was dissolved in 10 mL of THF and to this solution was added 5.0 mL of methanol and 1.0 g of NaOH. The reaction mixture was stirred for 15 min., 35 concentrated in vacuo and partitioned between a saturated aqueous solution of ammonium chloride (NH₄Cl) and ethyl acetate. The resulting aqueous layer was extracted twice with ethyl acetate. The ethylacetate layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by silica-gel chromatography (1:5 ethyl-acetate/hexane) to obtain 0.59 g (76 %) of the title compound as 40 a pale yellow solid, mp 145 °C (dec). LRMS: 230, 232 (M+2).

5

METHOD FCyclohexyl-methyl-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

The product from Method E (50 mg/0.218 mmol) was reacted with 0.12 mL of N-methylcyclohexylamine (0.920 mmol) as described in Method B. The reaction mixture was concentrate in vacuo, methanol was added, and the resulting precipitate filtered to provide 7 mg (10%) of the title compound as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ: 1.18-1.25 (m, 1H), 1.47-1.66 (m, 4H), 1.75-1.90 (m, 5H), 3.30 (s, 3H), 4.74 (br, 1H), 6.79 (s, 1H), 7.32-7.36 (m, 1H), 7.47-7.51 (m, 2H), 7.77 (d, 2H, J = 7.9 Hz), 8.33 (s, 1H). LRMS: 307 (M+1).

The title compound of Example 86 was prepared by a method analogous to that described in Example 85.

15

EXAMPLE 86(1H-Indol-5-yl)-(6-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

IH-Indolamine. LRMS: 326.4.

EXAMPLE 87Cyclohexyl-methyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

20

Cyclohexylmethylamine.

METHOD G7-Benzenesulfonyl-4-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine

To flame-dried flask under N₂ was charged 0.57 ml (4.07 mmol) of diisopropylamine and 5.0 mL of dry THF. The solution was cooled to -78 °C and 1.63 mL (4.08 mmol) of a 2.5 M solution of n-butyllithium in hexanes added. The resulting mixture was brought to 0 °C and stirred for 10 min. After cooling the mixture again to -78 °C, a solution of 1.0 g (3.40 mmol) of crude product from Method C in 10 mL of dry THF was added over a 10 min period. The resulting mixture was stirred for 1 h, at which time, 0.28 mL (4.50 mmol) of iodomethane were added. The reaction mixture was stirred for 2 h, quenched with a saturated solution of NH₄Cl and warmed to room temperature. The mixture was stirred for 5 min., diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over MgSO₄, filtered and evaporated in vacuo to obtain the title compound. LRMS: 308, 310 (M+2).

5

METHOD H4-Chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine

The product from Method G was deprotected as described in Method E. The crude product was purified by trituration with hexanes and dichloromethane to obtain 250 mg (44%) of the title compound as a yellow solid. Mp 205 °C dec. LRMS 168, 170 (M+2).

10

METHOD ICyclohexyl-methyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

The product from Method H (50 mg/0.298 mmol) was reacted with 100 mg (0.883 mmol) of N-methylcyclohexylamine as described in Method B. The reaction mixture was worked up as in Method B with the exception that ethyl acetate was used in place of ether.

- 15 The title compound (42 mg, 58 % yield) was obtained as a white solid. Mp 221 °C dec. ¹H NMR (400 MHz, CDCl₃) δ: 1.15-1.25 (m, 1H), 1.43-1.62 (m, 4H), 1.73 (br s, 1H, J = 13.7 Hz), 1.82-1.90 (m, 4H), 2.41 (d, 3H, J = 0.8 Hz), 3.21 (s, 3H) 4.63 (br s, 1H), 6.20 (s, 1H), 8.22 (s, 1H), 10.1 (br s, 1H). LRMS: 245 (M+1).

20 The title compound of Example 88 were prepared by a method analogous to that described in Example 87.

EXAMPLE 88Cyclohexyl-(6-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylamine. LRMS: 231.3.

EXAMPLE 894-Cyclohexyloxy-7H-pyrrolo[2,3-d]pyrimidineMETHOD L7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

- To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (250 mg/1.63 mmol) in 12 mL of DMF was added 676 mg (4.89 mmol) of potassium carbonate and the resulting 30 mixture stirred at room temperature for 20 min. Benzylchloride (310 mg/2.45 mmol) was added and the new mixture stirred at room temperature for 24 h then filtered, concentrated and the residue purified by silica gel chromatography (3:1 hexanes/ethyl acetate) affording 318 mg (80%) of the title compound. LRMS: 244.1 (M+1).

METHOD M7-Benzyl-4-cyclohexyloxy-7H-pyrrolo[2,3-d]pyrimidine

- To a flame dried flask under nitrogen was charged 84 mg (2.10 mmol) of 60 % sodium hydride in mineral oil and 3.0 mL of THF and the mixture cooled to 0 °C. Cyclohexanol (0.18 mL/1.70 mmol) was added and the reaction mixture stirred for 5 min. A solution of 102 mg (0.419 mmol) of the product from Method L in 1.0 mL of THF was added and the mixture 40 heated to reflux for 3 h. After cooling to room temperature, the reaction mixture was acidified

- 5 to pH 1 with 2 N HCl and concentrated in vacuo. The resulting residue was then slurried in ethyl acetate, filtered and the filtrate concentrated in vacuo to provide 76 mg (59%) of the title compound as an oil. LRMS: 308 (M+1).

METHOD N

4-Cyclohexyloxy-7H-pyrrolo[2,3-d]pyrimidine

- 10 To liquid ammonia (6.0 mL) at -78 °C was added 33 mg (1.43 mmol) sodium metal and the resulting dark blue solution stirred at -78 °C 10 min. A solution of 75 mg (0.244 mmol) of the product from Method M in 3.0 mL of ether was added dropwise over a 5 min period. The resulting solution stirred at -78 °C for 1 h followed by quenching upon addition of 500 mg of solid ammonium chloride. After evaporation at room temperature, the residual solid was
15 triturated with 25 mL of ethylacetate containing 1 mL of acetic acid for 1 h. Filtration and concentration in vacuo afforded crude material which was purified by preparative thin layer chromatography (silica-gel; 2:1 ethyl acetate/hexanes) to produce 5 mg of the title compound.
¹H NMR (400 MHz) (CDCl₃) δ: 1.27 - 1.35 (m, 6H), 1.62 - 1.67 (m, 4H), 5.30 - 5.36 (m, 1H),
6.55 (d, 1H, J = 3.2 Hz), 7.11 (d, 1H, J = 3.2 Hz), 8.37 (br s 1H). LRMS: 218.2 (M+1).

20

EXAMPLE 90

METHOD O

4-Cyclohexylsulfanyl-7H-pyrrolo[2,3-d]pyrimidine

- To a solution of 100 mg (0.651mmol) of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine dissolved in 3.0 mL of THF was added 0.10 mL (0.818 mmol) of cyclohexylmercaptan and 100
25 mg (0.847 mmol) of 95 % potassium tert-butoxide and the resulting mixture heated at reflux for 3.5 hr. After cooling to room temperature, the reaction mixture was acidified to pH 1 with 2 N HCl and concentrated in vacuo. The residue was then partitioned between ethylacetate and 1 N HCl. The aqueous layer was extracted with ethyl acetate, the ethyl acetate layers were combined, washed with brine, dried over MgSO₄, filtered, and evaporated in vacuo. The crude
30 product was purified by silica-gel chromatography (1:3 ethylacetate/hexanes) providing 34 mg (22%) of the title compound as a white solid. Mp 162-163 °C. ¹H NMR (400 MHz) d: 1.22-1.36 (m, 1H), 1.45-1.64 (m, 5H), 1.75-1.79 (m, 2H), 2.12-2.14 (m, 2H), 4.18-4.20 (m, 1H), 6.50 (d, 1H, J = 3.7 Hz), 7.19 (d, 1H, J = 3.5 Hz), 8.61 (s, 1H), 10.0 (br s, 1H). LRMS: 234 (M+1).

EXAMPLE 91

35

5-Chloro-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

5

METHOD R4,5-Dichloro-7H-pyrrolo[2,3-d]pyrimidine

4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (154 mg, 1.0 mmol) was suspended in 6.0 mL of dry dichloromethane in a flame-dried flask and to this mixture was added N-chlorosuccinimide (147 mg, 1.1 mmol) in one portion. The resulting mixture stirred at room temperature for 18 h, 10 at which time the solvent was removed under reduced pressure. The residue was triturated with water and isolated by filtration to afford 137 mg (72%) of the title compound as a gray solid, mp 224-227 °C(dec). LRMS: 188 (M+1).

METHOD S5-Chloro-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

15 The product from Method R (57 mg, 0.3 mmol) was suspended in 3.0 mL of tert-butanol and to this solution was added piperidine (90 μ L, 0.9 mmol) and the resulting system heated at reflux for 1 h. The reaction mixture was cooled to room temperature and water was added (4.0 mL). The solution was adjusted to pH 1 with 1 N HCl and then washed with ether. The aqueous layer was removed and adjusted to pH 12 with 2 N NaOH. The solution was 20 then extracted 2 x 15 mL with dichloromethane and the combined organics washed with water then brine and dried over MgSO₄. Evaporation of solvent afforded 45 mg of a yellow solid that was purified by silica-gel chromatography (3:1 ethyl acetate/hexanes) to yield 23 mg (32%) of the title compound as a light yellow solid. Mp 170 - 172 °C. ¹H NMR (400 MHz, CDCl₃) δ : 1.67 - 1.74 (m, 6H), 3.65 - 3.67 (m, 4H), 7.10 (s, 1H), 8.31 (s, 1H). LRMS: 237 (M + 1).

25 The title compounds of Examples 92-94 were prepared by a method analogous to that described in Example 91.

EXAMPLE 92(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(3-ethynyl-phenyl)-amine

3-Ethynylphenyl)amine. Melting Point: 250°C.

30

EXAMPLE 93(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-cycloheptyl-methyl-amine

Cycloheptylmethylamine. Melting Point: 152 - 153°C; LRMS: 279.8.

EXAMPLE 94(5-Chloro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-cyclooctyl-methyl-amine

35

Cyclooctylmethylamine. Melting Point: 151 - 153°C; LRMS: 293.8.

EXAMPLE 955-Phenyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

-40-

5

METHOD T

5-Bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (30 g/0.02 mol) dissolved in 75 mL of chloroform was added 3.5 g (0.02 mol) of N-bromosuccinamide and the resulting mixture refluxed for 1 h. After cooling to room temperature, the precipitate was removed by 10 filtration and dried under reduced pressure affording 4.1 g (89%) of the title compound. ¹H NMR (400 MHz) (CDCl₃) δ: 7.93 (d, 1H, J = 2.8 Hz), 8.60 (s, 1H).

METHOD U

7-Benzenesulfonyl-5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

To a slurry of the product from Method T (4.1 g/0.018 mol) in DMF (15 mL) and 15 cooled to 0 °C was added 1.0 g (0.025 mol) of 60% sodium hydride in mineral oil and the resulting mixture stirred at 0 °C for 15 min. Benzenesulfonyl chloride (3.2 g/0.018 mol) was added, the reaction mixture warmed to room temperature and stirred for 2 h. Water was then added (15 mL) and the resulting solid removed by filtration and dried in vacuo affording 5.9 g (89%) of the title compound.

20

METHOD V

7-BenzeneSulfonyl-5-bromo-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 2.0 g (5.37 mmol) of the product from Method U and 1.1 g (13.4 mmol) of piperidine in 10 mL of *tert*-butanol was heated with stirring at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was partitioned between dichloromethane (25 mL) and 25 water (25 mL). The dichloromethane layer was dried over sodium sulfate (Na₂SO₄) and concentrated to dryness in vacuo affording 2.2 g (97%) of the title compound. ¹H NMR (400 MHz) (CDCl₃) δ: 1.63 - 1.72 (m, 6H), 3.54 - 3.57 (m, 4H), 7.53 (t, 2H, J = 2.0 Hz), 7.60 (s, 1H), 7.61 (t, 1H, J = 2.0 Hz), 8.17 - 8.20 (m, 2H), 8.43 (s, 1H). LRMS: 422.7, 420.7 (M+1).

METHOD W

30

5-Phenyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of the product from Method V (100 mg/0.237 mmol) in 1.0 mL of dioxane was added 32 mg (0.261 mmol) of phenylboronic acid and 75 mg (0.356 mmol) of tribasic potassium phosphate followed by 7 mg (0.006 mmol) of tetrakis(triphenylphosphine) palladium. The resulting mixture was degassed with nitrogen and stirred at 100 °C for 48 h. 35 After cooling to room temperature, 1.0 mL of methanol was added followed by 50 mg of NaOH and the new mixture stirred at room temperature for 1 h. The resulting mixture was then partitioned between dichloromethane and water, the dichloromethane layer dried over MgSO₄ and concentrated to dryness in vacuo. The crude product was purified by silica-gel chromatography (2:1 ethyl acetate/hexanes) affording 13 mg (20%) of the title compound. 40 ¹H NMR (400 MHz) (CDCl₃) δ: 1.33 - 1.34 (m, 4H), 1.43 - 1.44 (m, 2H), 3.26 - 3.28 (m, 4H),

-41-

5 7.12 (s, 1H), 7.27 (t, 1H, J = 7.2 Hz), 7.38 (t, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 0.8 Hz), 8.42 (s, 1H). LRMS: 279.2 (M+1).

The title compounds of Examples 96-99 were prepared by a method analogous to that described in Example 95.

EXAMPLE 96

10 Cyclohexyl-methyl-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Cyclohexylmethylamine. Melting Point: 200°C; LRMS: 307.4.

EXAMPLE 97

Cyclohexyl-[5-(4-fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-methyl-amine

Cyclohexylmethylamine. Melting Point: 220°C; LRMS: 325.4.

15 Bicyclo[2.2.1]hept-2-yl-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine

Bicyclo[2.2.1]hept-2-yl-amine. LRMS: 305.4.

EXAMPLE 98

[5-(3-Chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-cyclohexyl-methyl-amine

20 Cyclohexyl-methylamine. LRMS: 455.9.

EXAMPLE 100

METHOD X

4-Piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (54 mg/0.3 mmol) (prepared by the method of Townsend, et. al., J. Am. Chem. Soc., 1969, 91, 2102) suspended in 3.0 mL tert-Butanol was added piperidine (59 µL/0.60 mmol). The resulting mixture was then heated at reflux for 2.5 h and after cooling to room temperature, was transferred to a separatory funnel and diluted with ether (20 mL). The solution was extracted 2 x 10 mL with 1N HCl, the combined aqueous layers were adjusted to pH 7 with 2 N potassium hydroxide (KOH) solution forming a precipitate which was collected by filtration, washed with water and dried under reduced pressure to give 29 mg (42%) of the title compound as a colorless solid. Mp 209 - 211 °C; ¹H NMR (400 MHz) (acetone-d6) δ: 1.72 - 1.74 (m, 6H), 3.72 - 3.79 (m, 4H), 8.12 (s, 1H), 8.29 (s, 1H). LRMS: 228 (M + 1).

EXAMPLE 101

35 5-Ethynyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

5

METHOD Y4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (30 g/0.02 mol) dissolved in 80 mL of chloroform was added 4.5 g (0.02 mol) of N-iodosuccinimide and the resulting mixture heated at reflux for 1 h. After cooling to room temperature, the precipitate was removed by filtration and dried under reduced pressure affording 4.6 g (82%) of the title compound.

METHOD Z7-Benzenesulfonyl-4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared as previously described in Method U using the product from Method X affording 5.4 g (80%) of material. LRMS: 419.6 (M+1), 279.7.

METHOD AA7-Benzenesulfonyl-5-iodo-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared by the procedure described in Method V using the product from Method Z to produce the title compound. LRMS: 469 (M+1), 329.1.

20

METHOD BB7-Benzenesulfonyl-4-piperidin-1-yl-5-triethylsilanyl lethynyl-7H-pyrrolo[2,3-d]pyrimidine

To a flamed-dried flask under nitrogen was charged 211 mg (0.5 mmol) of the product from Method AA, 19 mg (0.1 mmol) of copper (I) iodide and 58 mg (0.05 mmol) of tetrakis(triphenylphosphine)palladium. To this mixture was then added 0.14 mL (1.0 mmol) of triethylamine and 0.27 mL (1.5 mmol) of triethylsilylacetylene as a solution in 1.5 mL of dry DMF. The resulting mixture stirred at room temperature for 3 h, at which time, 5.0 mL of water were added and the mixture extracted with ethylacetate. The ethyl acetate extract was dried over MgSO₄ and concentrated in vacuo. The resulting crude product was then purified by silica-gel chromatography (7:1 hexanes/ethyl acetate) affording 194 mg (89%) of the title compound. LRMS: 481 (M+1), 341.

METHOD CC5-Ethynyl-4-piperidin-1-yl-7H-pyrrolo[2,3-d]pyrimidine

To a stirred solution of the product from Method BB (194 mg/0.40 mmol) dissolved in 2.0 mL of dry THF was added dropwise 0.4 mL (0.4 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The resulting mixture stirred at room temperature for 10 min, then was transferred to a methanol solution (3.0 mL) containing 1 g of KOH, the new mixture stirred at room temperature for 15 min. and concentrated in vacuo. The residue was partitioned between water and ethyl acetate, the ethyl acetate layer washed with water and brine, dried over MgSO₄ and concentrated to dryness in vacuo. The crude product was

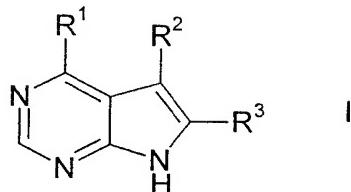
-43-

5 purified by silica-gel chromatography (2:1 ethyl acetate/hexanes) affording 72 mg (64%) of the title compound as a white crystalline solid. Mp 179 - 181 °C. ¹H NMR (400 MHz) (CDCl₃) δ: 1.72 (br s, 6H), 3.20 (s, 1H), 3.82 - 3.83 (m, 4H), 7.47 (s, 1H), 8.35 (s, 1H). LRMS: 227 (M+1).

5

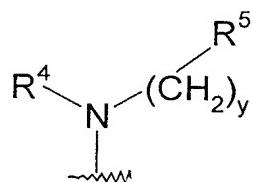
CLAIMS

1. A compound of the formula



or the pharmaceutically acceptable salt thereof; wherein

R¹ is a group of the formula

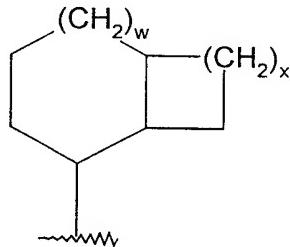


10

wherein y is 0, 1 or 2;

- R⁴ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;
- R⁵ is selected from the group consisting of trifluoromethyl(C₁-C₆)alkyl, (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, deuterium, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, halo, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R¹⁵R¹⁶NS(O)_m, R¹⁵R¹⁶NS(O)_m (C₁-C₆)alkyl, R¹⁵S(O)_m R¹⁶N, R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; or R⁵ is (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₂-C₆)alkoxy(C₁-C₆)alkyl,

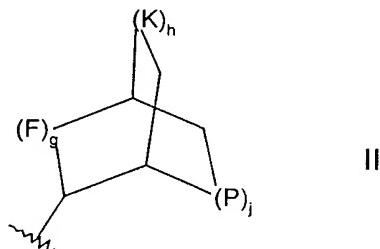
- 5 piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl,
(C₅-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio(C₁-C₆)alkyl,
(C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl,
(C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl
10 wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one to five cyano, nitro, halo, deuterium, hydroxy, carboxy, (C₁-C₆)acylamino, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, (C₁-C₆)alkylamino(C₁-C₆)acyl or ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl; or R⁵ is R¹³CO(C₁-C₆)alkyl or R¹³CO(C₃-C₁₀)cycloalkyl wherein R¹³ is R²⁰O or R²⁰R²¹N wherein R²⁰ and R²¹ are each independently selected from the group consisting of hydrogen, deuterium, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₅-C₉)heteroaryl(C₁-C₆)alkyl; or R⁵ is R¹⁴, R¹⁴(C₁-C₆)alkyl or R¹⁴(C₃-C₁₀)cycloalkyl wherein R¹⁴ is (C₂-C₉)heterocycloalkyl, (C₁-C₆)acylpiperazino, (C₆-C₁₀)aryl(piperazino, (C₅-C₉)heteroaryl(piperazino, (C₁-C₆)alkylpiperazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidinyl, (C₆-C₁₀)aryl(piperidyl, (C₅-C₉)heteroaryl(piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperidyl or (C₁-C₆)acylpiperidyl;
15 or R⁵ is a group of the formula



wherein w is 0, 1 or 2;

25 x is 0, 1, 2 or 3;

or R⁵ is a group of the formula



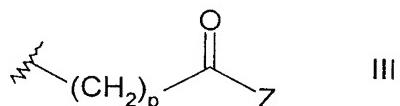
wherein g, h and j are each independently 0 to 3;

5 F, K and P are each independently oxygen, S(O)_d wherein d is 0, 1 or 2, NR⁶ or CR⁷R⁸;

R⁶ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl (difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)acyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₂-C₆)alkyl, (C₁-C₆)acyloxy(C₂-C₆)alkyl, (C₁-C₆)alkoxy(C₂-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)arylthio(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, R¹³CO(C₁-C₆)alkyl wherein R¹³ is R²⁰O or R²⁰R²¹N wherein R²⁰ and R²¹ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₅-C₉)heteroaryl(C₁-C₆)alkyl; or R¹⁴(C₂-C₆)alkyl wherein R¹⁴ is (C₁-C₆)acetylpirerazino, (C₆-C₁₀)arylpiperazino, (C₅-C₉)heteroarylpiperazino, (C₁-C₆)alkylpirerazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpirerazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpirerazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₅-C₉)heteroaryl(piperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiperidyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiperidyl, (C₁-C₆)alkoxyacyl, (C₁-C₆)alkylaminoaryl, ((C₁-C₆)alkyl)₂aminoacyl or (C₁-C₆)acetylpireridyl;

R⁷ and R⁸ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, amino, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)amino, (C₁-C₆)acylamino, (C₁-C₆)acyl(C₁-C₆)alkylamino, carboxy, (C₁-C₆)alkoxyacyl, (C₁-C₆)alkylaminoacyl, ((C₁-C₆)alkyl)₂aminoacyl, aminoacyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl (difluoromethylene), (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, piperazinyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₆-C₁₀)aryltio(C₁-C₆)alkyl, (C₁-C₆)alkylsulfinyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfinyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl(C₁-C₆)alkyl, (C₆-C₁₀)arylsulfonyl(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkyl, R¹³CO(C₁-C₆)alkyl or R¹³CO(C₃-C₁₀)cycloalkyl wherein R¹³ is R²⁰O or R²⁰R²¹N wherein R²⁰ and R²¹ are each independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl or (C₅-C₉)heteroaryl(C₁-C₆)alkyl; R¹⁴, R¹⁴(C₁-

- 5 C₆)alkyl or R¹⁴(C₃-C₁₀)cycloalkyl wherein R¹⁴ is (C₁-C₆)acetylperazino, (C₆-C₁₀)arylpiperazino, (C₅-C₉)heteroarylpirazino, (C₁-C₆)alkylpirazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpirazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpirazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C₁-C₆)alkylpiperidyl, (C₆-C₁₀)arylpiperidyl, (C₅-C₉)heteroarylpiridyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiridyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiridyl or (C₁-C₆)acetylpiridyl; or a group of the
10 formula



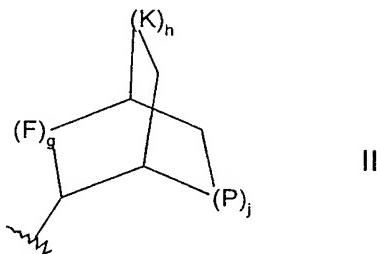
wherein p is 0, 1, 2 or 3; and

- Z is hydroxy, (C₁-C₆)alkoxy or NR¹R² wherein R¹ and R² are each independently
15 selected from the group consisting of hydrogen, (C₁-C₆)alkyl, piperidyl, (C₁-C₆)alkylpiridyl, (C₆-C₁₀)arylpiperidyl, (C₅-C₉)heteroarylpiridyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiridyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiridyl, (C₁-C₆)acetylpiridyl, (C₆-C₁₀)aryl, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₅-C₉)heteroaryl(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₆-C₁₀)aryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, R⁵(C₁-C₆)alkyl, (C₁-C₆)alkyl(CHR⁵)(C₁-C₆)alkyl wherein R⁵ is hydroxy, (C₁-C₆)acyloxy, (C₁-C₆)alkoxy, piperazino, (C₁-C₆)acylamino, (C₁-C₆)alkylthio, (C₆-C₁₀)arylthio, (C₁-C₆)alkylsulfinyl, (C₆-C₁₀)arylsulfinyl, (C₁-C₆)alkylsulfoxy, (C₆-C₁₀)arylsulfoxy, amino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, (C₁-C₆)acetylpirazino, (C₁-C₆)alkylpirazino, (C₆-C₁₀)aryl(C₁-C₆)alkylpirazino, (C₅-C₉)heteroaryl(C₁-C₆)alkylpirazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R⁶(C₁-C₆)alkyl, (C₁-C₅)alkyl(CHR⁶)(C₁-C₆)alkyl wherein R⁶ is piperidyl, (C₁-C₆)alkylpiridyl, (C₆-C₁₀)arylpiperidyl, (C₆-C₁₀)aryl(C₁-C₆)alkylpiridyl, (C₅-C₉)heteroaryl(C₁-C₆)alkylpiridyl;

or R¹ is defined as OR⁹ or S(O)_qR⁹ wherein q is 0, 1 or 2; and

- R⁹ is selected from the group consisting of trifluoromethyl(C₁-C₆)alkyl, (C₁-C₃)alkyl(difluoromethylene)(C₁-C₃)alkyl, (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five carboxy, cyano, amino, hydroxy, (C₁-C₆) alkoxy, halo, (C₁-C₆)alkyl S(O)_m wherein m is 0, 1 or 2; R¹⁵R¹⁶NS(O)_m wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl; (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, R¹⁵R¹⁶N-CO-O-, R¹⁵R¹⁶N-
30 CO-(C₁-C₆)alkyl wherein R¹⁵ and R¹⁶ are as defined above; (C₂-C₆)alkenyl, (C₂-C₆) alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)

- 5 C_6)acyl, (C_1-C_6) alkylamino(C_1-C_6)acyl or $((C_1-C_6)$ alkyl) $_2$ amino(C_1-C_6)acyl; (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_{10}) cycloalkyl(C_1-C_6)alkyl, (C_1-C_6) acyloxy(C_1-C_6)alkyl, (C_2-C_6) alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6) alkylamino(C_1-C_6)alkyl, (C_6-C_{10}) aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9) heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6) alkylthio(C_1-C_6)alkyl, (C_6-C_{10}) arylothio(C_1-C_6)alkyl, (C_1-C_6) alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10}) arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6) alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10}) arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6) alkylamino(C_1-C_6)alkyl, $((C_1-C_6)$ alkyl) $_2$ amino, (C_1-C_6) alkyl wherein the alkyl group is optionally substituted by one to five cyano, nitro, hydroxy, carboxy, (C_1-C_6) acylamino, (C_1-C_6) alkoxy(C_1-C_6)acylamino, amino(C_1-C_6)acyl, (C_1-C_6) alkylamino(C_1-C_6)acyl or $((C_1-C_6)$ alkyl) $_2$ amino(C_1-C_6)acyl; $R^{13}CO(C_1-C_6)$ alkyl or $R^{13}CO(C_3-C_{10})$ cycloalkyl wherein R^{13} is $R^{20}O$
- 10 or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6) alkyl, (C_6-C_{10}) aryl(C_1-C_6)alkyl or (C_5-C_9) heteroaryl(C_1-C_6)alkyl; R^{14} , $R^{14}(C_1-C_6)$ alkyl or $R^{14}(C_3-C_{10})$ cycloalkyl wherein R^{14} is (C_2-C_9) heterocycloalkyl, (C_1-C_6) acylpiperazino, (C_6-C_{10}) arylpiperazino, (C_5-C_9) heteroarylpiperazino, (C_1-C_6) alkylpiperazino, (C_6-C_{10}) aryl(C_1-C_6)alkylpiperazino, (C_5-C_9) heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6) alkylpiperidinyl, (C_6-C_{10}) arylpiperidyl, (C_5-C_9) heteroarylpiperidyl, (C_6-C_{10}) aryl(C_1-C_6)alkylpiperidyl or (C_1-C_6) acylpiperidyl;
- 15 or R^9 is a group of the formula



25 wherein g, h and j are each independently 0 to 6;

F, K and P are each independently oxygen, $S(O)_d$ wherein d is 0, 1 or 2, NR^6 or CR^7R^8 wherein R^6 , R^7 and R^8 are as defined above;

20 R^2 and R^3 are each independently selected from the group consisting of hydrogen, deuterium, amino, halo, hydroxy, nitro, carboxy, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, trifluoromethyl, trifluoromethoxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy wherein the alkyl or alkoxy groups are optionally substituted by one to three groups selected from halo, hydroxy, carboxy, amino (C_1-C_6)alkylthio, (C_1-C_6) alkylamino, $((C_1-C_6)$ alkyl) $_2$ amino, (C_5-C_9) heteroaryl, (C_2-C_9) heterocycloalkyl, (C_3-C_9) cycloalkyl or (C_6-C_{10}) aryl; or R^2 and R^3 are each independently (C_3-C_{10}) cycloalkyl, (C_3-C_{10}) cycloalkoxy, (C_1-C_6) alkylamino, $((C_1-C_6)$ alkyl) $_2$ amino, (C_6-C_{10}) arylpiperidinyl, (C_6-C_{10}) arylpiperazino, (C_6-C_{10}) arylpiperidyl, (C_5-C_9) heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6) acylpiperidyl;

- 5 $\text{C}_{10}\text{)aryl}$ amino, $(\text{C}_1\text{-}\text{C}_6)\text{alkylthio}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylthio}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfinyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylsulfinyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfonyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylsulfonyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{acyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy-CO-NH-}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino-CO-}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}$, $(\text{C}_2\text{-}\text{C}_9)\text{heterocycloalkyl}$ or $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}$ wherein the heteroaryl, heterocycloalkyl and aryl groups are optionally substituted by one to three halo, $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkyl-CO-NH-}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy-CO-NH-}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkyl-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy-(C}_1\text{-}\text{C}_6\text{)alkoxy}$, carboxy , $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}$, $\text{benzyloxycarbonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}$, amino , $\text{amino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonylamino}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonylamino}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, hydroxy , $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}$, carboxy , $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy-CO-NH-}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkyl-CO-NH-}$, cyano , $(\text{C}_5\text{-}\text{C}_9)\text{heterocycloalkyl}$, amino-CO-NH- , $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino-CO-NH-}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino-CO-NH-}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylamino-CO-NH-}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroarylamino-CO-NH-}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{arylamino-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroarylamino-CO-NH-(C}_1\text{-}\text{C}_6\text{)alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfonyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfonylamino}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylsulfonylamino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl sulfonyl}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl sulfonylamino}$, $(\text{C}_6\text{-}\text{C}_{10})\text{aryl sulfonylamino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}$ or $(\text{C}_2\text{-}\text{C}_9)\text{heterocycloalkyl}$;
- with the proviso that when either R^4 and R^5 is hydrogen, the other of R^4 or R^5 cannot be $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}$ or $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$;
- with the proviso that when R^4 is hydrogen, unsubstituted $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ or unsubstituted $(\text{C}_3\text{-}\text{C}_{10})\text{cycloalkyl}$, R^5 cannot be $(\text{C}_6\text{-}\text{C}_{10})\text{aryl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$; R^{20} and R^{21} cannot be $(\text{C}_5\text{-}\text{C}_9)\text{heteroaryl}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$; and R^{14} cannot be $(\text{C}_2\text{-}\text{C}_9)\text{heterocycloalkyl}$, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidinyl or $(\text{C}_1\text{-}\text{C}_6)\text{alkylpiperidinyl}$;
- with the proviso that the sp^2 and sp carbons of alkenyl or alkynyl cannot be substituted by hydroxy or amino;
- with the proviso that when R^4 is hydrogen, R^5 cannot be amino $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $(\text{C}_1\text{-}\text{C}_6)\text{alkylamino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, $((\text{C}_1\text{-}\text{C}_6)\text{alkyl})_2\text{amino}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, furanyl, $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ or $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$;
- with the proviso that both R^4 and R^5 cannot both be hydroxy $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$;
- with the proviso that when R^4 is $(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$, R^5 cannot be $(\text{C}_1\text{-}\text{C}_6)\text{alkoxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$ or $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkyl}$; and
- with the proviso that R^1 cannot be $\text{carboxy}(\text{C}_1\text{-}\text{C}_6)\text{alkylthio}$ or $(\text{C}_1\text{-}\text{C}_6)\text{alkoxycarbonyl}(\text{C}_1\text{-}\text{C}_6)\text{alkylthio}$.
2. A compound according to claim 1, wherein R^1 is NR^4R^5 .

- 5 3. A compound according to claim 1, wherein R⁴ is hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by hydroxy, amino, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino or (C₁-C₆)acylamino; or R⁴ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by hydroxy, trifluoromethyl or (C₁-C₆)acyloxy.
- 10 4. A compound according to claim 1, wherein R⁵ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by one to five deuterium, hydroxy, trifluoromethyl, halo, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)acyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, (C₁-C₆)acylamino, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, halo(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, R¹⁵S(O)_m R¹⁶N,
- 15 R¹⁵S(O)_mR¹⁶N(C₁-C₆)alkyl wherein m is 0, 1 or 2 and R¹⁵ and R¹⁶ are each independently selected from hydrogen or (C₁-C₆)alkyl.
- 20 5. A compound according to claim 1, wherein R² and R³ are each independently selected from the group consisting of hydrogen, halo, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₁₀)cycloalkyl, (C₃-C₁₀)cycloalkoxy, (C₂-C₉)heterocycloalkyl, (C₅-C₉)heteroaryl or (C₆-C₁₀)aryl.
- 25 6. A compound according to claim 1, wherein said compound is selected from the group consisting of:
- 2-{4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohexyl}-propan-2-ol;
- 25 2-{3-[(2-Hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-4-methyl-cyclohexyl}-propan-2-ol;
- 2-{5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
- 30 (5-Isopropenyl-2-methyl-cyclohexyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoroethyl)-amine;
- 2-{4-Methyl-3-[(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(2,2,2-trifluoro-ethyl)-amino]-cyclohexyl}-propan-2-ol;
- 2-{4-Methyl-5-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclohex-3-enyl}-propan-2-ol;
- 35 2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-3-yl]-propan-2-ol;
- 2-[1-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-azetidin-2-yl]-propan-2-ol;
- (5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-(5-isopropenyl-2-methyl-cyclohexyl)-methyl-amine;
- 2-{3-[(5-Fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-methyl-amino]-4-methyl-cyclohexyl}-
- 40 propan-2-ol;

- 5 (2-Ethyl-4-isopropenyl-cyclopentyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine;
2-{3-Ethyl-4-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-propan-2-ol;
2-{3-Ethyl-4-[(2-hydroxy-ethyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-cyclopentyl}-
propan-2-ol;
2-[(2-Ethyl-4-isopropenyl-cyclopentyl)-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-
10 ethanol;
 (5-(S)-Isopropenyl-2-methyl-cyclohexyl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-
amine;
 3-Methyl-8-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-8-aza-bicyclo[3.2.1]octan-3-ol;
 2-[Cycloheptyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
15 2-[Cyclooctyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-ethanol;
 Bicyclo[2.2.1]hept-2-yl-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine; and
 4-Piperidin-1-yl-5-m-tolyl-7H-pyrrolo[2,3-d]pyrimidine.
7. A pharmaceutical composition for (a) treating or preventing a disorder or
condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid
20 arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic
dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's
disease, leukemia and other autoimmune diseases or (b) the inhibition of protein tyrosine
kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of
a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such
25 disorders or conditions and a pharmaceutically acceptable carrier.
8. A pharmaceutical composition for (a) treating or preventing a disorder or
condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid
arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic
dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's
30 disease, leukemia and other autoimmune diseases or (b) the inhibition of protein tyrosine
kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising an amount of
a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination
with one or more additional agents which modulate a mammalian immune system or with
antiinflammatory agents, effective in such disorders or conditions and a pharmaceutically
35 acceptable carrier.
9. A method for the inhibition of protein tyrosine kinases or Janus Kinase 3
(JAK3) in a mammal, including a human, comprising administering to said mammal an
effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.
10. A method for treating or preventing a disorder or condition selected from
40 organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I

- 5 diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.
- 10 11. A method for the inhibition of protein tyrosine kinases or Janus Kinase 3 (JAK3) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents.
- 15 12. A method for treating or preventing a disorder or condition selected from organ transplant rejection, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases in a mammal, including a human, comprising administering to said 20 mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, alone or in combination with one or more additional agents which modulate a mammalian immune system or with antiinflammatory agents, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Inter'nal Application No
PCT/IB 99/01100

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/04 A61K31/505 // (C07D487/04, 239:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 02266 A (CIBA-GEIGY AG) 23 January 1997 (1997-01-23) the whole document ----	1-12
Y	WO 98 07726 A (NOVARTIS AG) 26 February 1998 (1998-02-26) the whole document ----	1-12
Y	EP 0 682 027 A (CIBA-GEIGY AG) 15 November 1995 (1995-11-15) the whole document ----	1-12
Y	EP 0 795 556 A (PHARMACIA & UPJOHN S.P.A.) 17 September 1997 (1997-09-17) the whole document ----	1-12 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

16 September 1999

24/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

INTERNATIONAL SEARCH REPORTInter'nal Application No
PCT/IB 99/01100**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 23613 A (PFIZER INC.) 4 June 1998 (1998-06-04) the whole document -----	1-12
Y	WO 96 40142 A (PFIZER INC.) 19 December 1996 (1996-12-19) the whole document -----	1-12

INTERNATIONAL SEARCH REPORT

I. International application No.

PCT/IB 99/01100

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 9-12 because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members				International Application No PCT/IB 99/01100
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9702266	A 23-01-1997	AU 707626	B	15-07-1999
		AU 6414896	A	05-02-1997
		CA 2224435	A	23-01-1997
		CZ 9800015	A	15-04-1998
		EP 0836605	A	22-04-1998
		HU 9900330	A	28-05-1999
		NO 975956	A	10-02-1998
		NZ 312665	A	30-08-1999
		PL 324285	A	11-05-1998
		SI 9620103	A	31-10-1998
		SK 398	A	08-07-1998
		ZA 9605723	A	06-01-1997
WO 9807726	A 26-02-1998	AU 4206497	A	06-03-1998
		EP 0938486	A	01-09-1999
EP 682027	A 15-11-1995	AT 159257	T	15-11-1997
		AU 695244	B	13-08-1998
		AU 1772295	A	09-11-1995
		CA 2148324	A	04-11-1995
		CN 1128263	A	07-08-1996
		CZ 9501131	A	13-12-1995
		DE 59500788	D	20-11-1997
		DK 682027	T	04-05-1998
		ES 2109796	T	16-01-1998
		FI 952033	A	04-11-1995
		GR 3025158	T	27-02-1998
		HK 1002935	A	25-09-1998
		HU 71818	A	28-02-1996
		JP 8053454	A	27-02-1996
		NO 951684	A	06-11-1995
		NZ 272031	A	29-01-1997
		PL 308426	A	13-11-1995
		SK 56195	A	08-05-1996
		US 5686457	A	11-11-1997
		ZA 9503495	A	03-11-1995
EP 795556	A 17-09-1997	JP 9323995	A	16-12-1997
WO 9823613	A 04-06-1998	AU 4718997	A	22-06-1998
		HR 970641	A	31-10-1998
		NO 992524	A	26-05-1999
WO 9640142	A 19-12-1996	CA 2223081	A	19-12-1996
		HU 9601559	A	28-02-1997
		AP 637	A	08-04-1998
		AU 5479196	A	19-12-1996
		BR 9602695	A	06-10-1996
		CN 1141298	A	29-01-1997
		CZ 9601641	A	11-12-1996
		EP 0831829	A	01-04-1998
		FI 974443	A	05-12-1997
		HR 960269	A	31-08-1997
		JP 10508875	T	02-09-1998
		NO 962386	A	09-12-1996
		NZ 286755	A	25-03-1998
		PL 314641	A	09-12-1996
		SG 45483	A	16-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/01100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640142 A		SI 9600184 A SK 72996 A TR 961053 A	30-04-1997 09-04-1997 21-12-1996